THE LANCET
Oncology

Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Locke FL, Ghobadi A, Jacobson CA, et al. Long-term safety and activity of axicabtagene ciloleucel in refractory large B-cell lymphoma (ZUMA-1): a single-arm, multicentre, phase 1–2 trial. *Lancet Oncol* 2018; published online Dec 2. http://dx.doi.org/10.1016/S1470-2045(18)30864-7.

Supplementary Appendix

Long-term safety and activity of axicabtagene ciloleucel (anti-CD19 CAR T) in refractory large B-cell lymphoma (ZUMA-1): a multicentre, single arm, phase 1-2 trial
Locke, et al

Contents

Methods

Full listing of study sites

Center	Lead Investigator	No. Patients
The University of Texas MD Anderson Cancer Center, Houston, TX, USA	Dr. Sattva Neelapu	24
Moffitt Cancer Center & Research Institute, Tampa, FL, USA	Dr. Frederick Locke	23
Washington University, St. Louis, MO, USA	Dr. Nancy Bartlett	12
Dana-Farber Cancer Institute, Boston, MA, USA	Dr. Caron Jacobson	8
Stanford University, Stanford, CA, USA	Dr. David Miklos	7
University of Miami, Miami, FL, USA	Dr. Lazaros Lekakis	7
Montefiore Medical Center, Bronx, NY, USA	Dr. Ira Braunschweig	5
Vanderbilt University Medical Center, Nashville, TN, USA	Dr. Olalekan Oluwole	5
City of Hope National Medical Center, Duarte, CA, USA	Dr. Tanya Siddiqi	4
Loyola University Medical Center, Maywood, IL, USA	Dr. Patrick Stiff	3
Mayo Clinic, Rochester, MN, USA	Dr. Yi Lin	3
University of California at Los Angeles, Los Angeles, CA, USA	Dr. John Timmerman	3
Sarah Cannon Research Institute, Nashville, TN, USA	Dr. Ian Flinn	2
University of Rochester School of Medicine, Rochester, NY, USA	Dr. Patrick Reagan	2
Karmanos Cancer Center, Wayne State University, Detroit, MI, USA	Dr. Abhinav Deol	2
Cleveland Clinic, Cleveland, OH, USA	Dr. Brian Hill	2
John Theurer Cancer Center, Hackensack University Medical Center, Hackensack, NJ, USA	Dr. Andre Goy	2
Sarah Cannon Research Institute, Denver, CO, USA	Dr. Peter McSweeney	1
Holden Comprehensive Cancer Center, Iowa City, IA, USA	Dr. Umar Farooq	1
Banner MD Anderson Cancer Center, Gilbert, AZ, USA	Dr. Javier Munoz	1
University of California at San Diego, San Diego, CA, USA	Dr. Dimitrios Tzachanis	1
Tel-Aviv Sourasky Medical Center, Tel-Aviv, Israel	Dr. Irit Avivi	1

Definition of secondary endpoints

Objective response rate per Independent Central Review Committee was defined as the combined rates of complete and partial responses any time on study, by Independent Central Review Committee according to the revised International Working Group Response Criteria for Malignant Lymphoma.[1]

Duration of response for patients who achieve an objective response was defined as the date of first objective response to disease progression per the revised International Working Group Response Criteria for Malignant Lymphoma[1] or death regardless of cause.

Progression-free survival was defined as the time from the axicabtagene ciloleucel infusion date to the date of disease progression per the revised International Working Group Response Criteria for Malignant Lymphoma[1] or death from any cause.

Overall survival was defined as the time from axicabtagene ciloleucel infusion to the date of death.

Incidence of adverse events and clinically significant changes in safety lab values were assessed as described above.

Levels of anti-CD19 CAR T cells in blood, levels of cytokines in serum and incidence of anti-axicabtagene ciloleucel antibodies were summarized.

Cell of origin

Cell of origin subtype was centrally assessed retrospectively by the NanoString Lymphoma Subtyping Test.[2]

B-cell quantification

B-cell recovery in blood was evaluated post hoc by flow cytometry using cryopreserved peripheral blood mononuclear cells in all patients with ongoing responses for whom baseline values were available. B cells were defined as expressing CD19, CD20, or both B-cell–lineage cell surface antigens.

B-cell levels were assessed by flow cytometric of analysis of peripheral blood and defined as live $CD45^+$, $CD4^–$, $CD14^–$, $CD3^–$, $CD16^–$, $CD56^–$, and $CD19^+$ and/or $CD20^+$ lymphocytes. Live cells were distinguished with LIVE/DEAD Aqua Fixable Viability Stain (Thermo Fisher; Waltham, MA). The following Biolegend (San Diego, CA) antibodies were used: CD45 APC-Fire750 (clone 2D1), CD19 PE (clone HIB19), CD20 BV421 (clone 2H7), CD4 PerCP-Cy5.5 (clone RPA-T4), CD14 Alexa488 (clone HCD14), CD3 PE-Cy7 (clone UCHT1), CD16 APC (clone 3G8), CD56 APC (clone HCD56). Samples were acquired on a BD LSRII using FACSDiva software (BD Biosciences) and analyzed with FlowJo software (Tree Star; Ashland, Oregon). The lower limit of quantification of the assay was 17 B cells per 100,000 viable leukocytes (0·017%).

Determination of patients with double-expressor and high-grade B-cell lymphoma (DE/HGBCL)

DE/HGBCL status was determined retrospectively by blinded, central pathology review. Double-expressor B-cell lymphoma was defined as MYC+ [⩾ 40%] and BCL-2+ [⩾ 50%] by protein expression using immunohistochemistry [IHC]. High-grade B-cell lymphoma was assessed morphologically and further defined as double- or triple-hit (MYC+ and BCL2+ and/or BCL6+, respectively, by fluorescence in situ hybridization [FISH]).[3] For samples that were morphologically consistent with HGBCL and negative for MYC by FISH, Ki67 expression was evaluated by immunohistochemistry. Samples that were MYC-negative and > 70% Ki67-positive) were categorized as HGBCL not otherwise specified (NOS).[4]

Analysis of progression-free survival by response at three months

In a post hoc analysis, patients from phase 2 of ZUMA-1 were analyzed by response status (stable disease, partial response, or complete response) at three months after axicabtagene ciloleucel infusion, and Kaplan-Meier curves of progression-free survival were generated for patients with complete response, partial response, or stable disease at three months to assess long-term (at least two-year) responses.

Results

Summary of protocol deviations

A total of 22 protocol deviations were reported for 19 patients. None of these deviations were considered important protocol deviations and did not have any impact on primary endpoints or secondary endpoints of the study or patient safety. The most frequently occurring relevant protocol deviation was off-schedule procedures, including baseline positron emission tomography–computed tomography (PET-CT) not performed within 28 days of conditioning chemotherapy (12 deviations) or on-study scan not performed per protocol time (two deviations).

Use of medications that were to be excluded per protocol, between the time of leukapheresis and prior to infusion of axicabtagene ciloleucel (Day 0) were not considered important protocol deviations because all of these were considered prophylactic or medically necessary, but two patients received steroids within seven days of leukapheresis and five received steroids within five days of axicabtagene ciloleucel dosing. Lastly, four patients did not initially meet the study eligibility criteria due to compromised end organ function at screening (two patients), prior hepatitis C infection (one patient), and prior palliative radiotherapy to a non-target lesion at screening (one patient).

Table 1. **Baseline characteristics for patients with DE/HGBCL on phase 1 and phase 2.**

Characteristic	DE/HGBCL (n=37)
Median age, years (IQR)	60 (51–64)
Age ⩾ 65	9 (24)
Male,	25 (68)
ECOG PS	
0	15 (41)
1	22 (59)
Disease stage	
I or II	8 (22)
III or IV	29 (78)
IPI score 3 – 4	
0-2	22 (59)
3-4	15 (41)
High-grade B-cell lymphoma only*	7 (19)
Prior therapies	
Median (IQR)	3 (3–4)
1	0
2	9 (24)
⩾3	28 (76)
Refractory Subgroup Before Enrollment	
Primary refractory	0
Refractory to second- or later-line therapy	29 (78)
Best response as PD to last prior therapy	22 (59)
Relapse after autologous stem cell transplantation	8 (22)

Data are number (%), unless otherwise indicated.
BCL=B-cell lymphoma. DE/HGBCL=double expressor and high-grade B-cell lymphoma. ECOG PS=Eastern Cooperative Oncology Group performance status. IHC=immunohistochemistry. IPI=International Prognostic Index. IQR=interquartile range. MYC, myelocytomatosis viral oncogene. PD=progressive disease.
*High-grade B-cell lymphoma was defined as double- or triple-hit (MYC+ and BCL2+ and/or BCL6+ by fluorescence in situ hybridization) or not otherwise specified (MYC– and > 70% Ki67 by IHC).

Table 2. **Objective and ongoing responses for the phase 2 intent-to-treat population by investigator assessment.**

Response*	**ITT (N=111)**
ORR (CR/PR)	84 (76)
CR	59 (53)
PR	25 (23)
Ongoing Response	39 (35)
Ongoing CR	37 (33)
Ongoing PR	2 (2)

Data are number (%), unless otherwise indicated.
*Response was assessed using the International Working Group Response Criteria for Malignant Lymphoma[1] at month 1, every three months from month 3 to month 24, and as clinically indicated and/or per the institution's standard of care after two years.
CR=complete response. ORR=objective response rate.
PR=partial response.

Table 3. **Objective and ongoing responses for phase 2 patients with DE/HGBCL by investigator assessment.**

	HGBCL: MYC+, BCL2+, BCL6+ (Triple Hit by FISH) (n=1)	**HGBCL: MYC+, BCL2+ or BCL6+ (Double Hit by FISH) (n=3)**	**HGBCL NOS: MYC- (by FISH), Ki67 >70% (by IHC) (n=2)**	**Overall HGBCL (n=6)**	**Co-expression of MYC and BCL2 (double expressor lymphoma by IHC) (n=27)**	**Overall (n=33)**
ORR (CR/PR)	1 (100)	3 (100)	2 (100)	6 (100)	24 (89)	30 (91)
CR	1 (100)	2 (67)	1 (50)	4 (67)	19 (70)	23 (70)
PR	0	1 (33)	1 (50)	2 (33)	5 (19)	7 (21)
Ongoing Response	1 (100)	1 (33)	0	2 (33)	14 (52)	16 (48)
Ongoing CR	1 (100)	1 (33)	0	2 (33)	14 (52)	16 (48)
Ongoing PR	0	0	0	0	0	0

Data are number (%), unless otherwise indicated.
BCL=B-cell lymphoma; CR=complete response; DE/HGBCL=double expressor and high-grade B-cell lymphoma. FISH=fluorescence in situ hybridization HGBCL=high grade B-cell lymphoma; IHC, immunohistochemistry; NOS=not otherwise specified; ORR=objective response rate; PR=partial response.

***Table 4*. Safety summary for all 108 patients treated on phase 1 and phase 2.**

Treatment-Emergent Adverse Events	Worst Grade 1/2	Worst Grade 3	Worst Grade 4	Worst Grade 5
Any adverse event	2 (2)	28 (26)	69 (64)	9 (8)*
Axicabtagene ciloleucel-related	36 (33)	53 (49)	16 (15)	2 (2)
Serious adverse events	8 (7)	34 (31)	9 (8)	9 (8)
Neurologic events	37 (34)	32 (30)	3 (3)	0
Cytokine release syndrome	88 (81)	7 (6)	4 (4)	1 (1)

Data are number (%).
*Five deaths were due to disease progression.

***Table 5*. Treatment-emergent adverse event by grade for all 108 patients treated on phase 1 and phase 2.**

Adverse Event	Any	Worst Grade 1	Worst Grade 2	Worst Grade 3	Worst Grade 4	Worst Grade 5
Any	108 (100)	0 (0)	2 (2)	28 (26)	69 (64)	9 (8)
Pyrexia	94 (87)	17 (16)	62 (57)	15 (14)	0 (0)	0 (0)
Anaemia	73 (68)	4 (4)	20 (19)	46 (43)	3 (3)	0 (0)
Hypotension	63 (58)	19 (18)	29 (27)	14 (13)	1 (1)	0 (0)
Nausea	63 (58)	42 (39)	21 (19)	0 (0)	0 (0)	0 (0)
Fatigue	57 (53)	32 (30)	22 (20)	3 (3)	0 (0)	0 (0)
Decreased appetite	55 (51)	37 (34)	16 (15)	2 (2)	0 (0)	0 (0)
Headache	50 (46)	40 (37)	9 (8)	1 (1)	0 (0)	0 (0)
Diarrhoea	48 (44)	33 (31)	10 (9)	5 (5)	0 (0)	0 (0)
Neutropenia	48 (44)	1 (1)	5 (5)	10 (9)	32 (30)	0 (0)
Hypoalbuminaemia	43 (40)	17 (16)	25 (23)	1 (1)	0 (0)	0 (0)
Hypocalcaemia	43 (40)	20 (19)	16 (15)	7 (6)	0 (0)	0 (0)
Tachycardia	43 (40)	38 (35)	3 (3)	2 (2)	0 (0)	0 (0)
Chills	40 (37)	33 (31)	7 (6)	0 (0)	0 (0)	0 (0)
Encephalopathy	40 (37)	11 (10)	4 (4)	23 (21)	2 (2)	0 (0)
Febrile neutropenia	39 (36)	0 (0)	4 (4)	33 (31)	2 (2)	0 (0)
Hyponatraemia	38 (35)	25 (23)	1 (1)	12 (11)	0 (0)	0 (0)
Thrombocytopenia	38 (35)	6 (6)	6 (6)	11 (10)	15 (14)	0 (0)
Vomiting	37 (34)	30 (28)	6 (6)	1 (1)	0 (0)	0 (0)
Hypokalaemia	36 (33)	26 (24)	7 (6)	3 (3)	0 (0)	0 (0)
Neutrophil count decreased	36 (33)	0 (0)	1 (1)	7 (6)	28 (26)	0 (0)
Hypoxia	34 (31)	1 (1)	21 (19)	11 (10)	1 (1)	0 (0)
Tremor	33 (31)	27 (25)	4 (4)	2 (2)	0 (0)	0 (0)
White blood cell count decreased	33 (31)	1 (1)	1 (1)	3 (3)	28 (26)	0 (0)
Constipation	32 (30)	24 (22)	8 (7)	0 (0)	0 (0)	0 (0)
Platelet count decreased	32 (30)	9 (8)	6 (6)	8 (7)	9 (8)	0 (0)
Cough	31 (29)	25 (23)	6 (6)	0 (0)	0 (0)	0 (0)
Hypophosphataemia	31 (29)	6 (6)	5 (5)	18 (17)	2 (2)	0 (0)
Confusional state	29 (27)	8 (7)	11 (10)	10 (9)	0 (0)	0 (0)
Dizziness	23 (21)	21 (19)	2 (2)	0 (0)	0 (0)	0 (0)
Dyspnoea	23 (21)	16 (15)	5 (5)	2 (2)	0 (0)	0 (0)
Alanine aminotransferase increased	22 (20)	11 (10)	5 (5)	5 (5)	1 (1)	0 (0)
Lymphocyte count decreased	22 (20)	0 (0)	0 (0)	2 (2)	20 (19)	0 (0)
Oedema peripheral	21 (19)	15 (14)	6 (6)	0 (0)	0 (0)	0 (0)
Sinus tachycardia	21 (19)	16 (15)	5 (5)	0 (0)	0 (0)	0 (0)
Hyperglycaemia	20 (19)	5 (5)	10 (9)	5 (5)	0 (0)	0 (0)
Hypomagnesaemia	20 (19)	19 (18)	1 (1)	0 (0)	0 (0)	0 (0)
Leukopenia	20 (19)	0 (0)	2 (2)	5 (5)	13 (12)	0 (0)
Aphasia	19 (18)	5 (5)	6 (6)	8 (7)	0 (0)	0 (0)
Aspartate aminotransferase increased	19 (18)	10 (9)	2 (2)	7 (6)	0 (0)	0 (0)
Somnolence	18 (17)	3 (3)	6 (6)	8 (7)	1 (1)	0 (0)
Hypertension	17 (16)	2 (2)	7 (6)	8 (7)	0 (0)	0 (0)
Muscular weakness	17 (16)	9 (8)	7 (6)	1 (1)	0 (0)	0 (0)
Pleural effusion	17 (16)	9 (8)	6 (6)	2 (2)	0 (0)	0 (0)
Weight decreased	17 (16)	7 (6)	10 (9)	0 (0)	0 (0)	0 (0)
Abdominal pain	16 (15)	10 (9)	4 (4)	2 (2)	0 (0)	0 (0)
Back pain	16 (15)	10 (9)	5 (5)	1 (1)	0 (0)	0 (0)
Hypogammaglobulinaemia	16 (15)	8 (7)	8 (7)	0 (0)	0 (0)	0 (0)
Myalgia	16 (15)	13 (12)	2 (2)	1 (1)	0 (0)	0 (0)
Anxiety	15 (14)	10 (9)	4 (4)	1 (1)	0 (0)	0 (0)
Dehydration	13 (12)	5 (5)	5 (5)	3 (3)	0 (0)	0 (0)
Dry mouth	13 (12)	13 (12)	0 (0)	0 (0)	0 (0)	0 (0)
Insomnia	13 (12)	8 (7)	5 (5)	0 (0)	0 (0)	0 (0)
Pain in extremity	13 (12)	8 (7)	5 (5)	0 (0)	0 (0)	0 (0)
Arthralgia	11 (10)	7 (6)	4 (4)	0 (0)	0 (0)	0 (0)
Agitation	10 (9)	3 (3)	2 (2)	5 (5)	0 (0)	0 (0)
Lymphopenia	10 (9)	0 (0)	2 (2)	1 (1)	7 (6)	0 (0)
Pneumonia	10 (9)	0 (0)	3 (3)	7 (6)	0 (0)	0 (0)
Asthenia	9 (8)	2 (2)	5 (5)	2 (2)	0 (0)	0 (0)
Atrial fibrillation	9 (8)	1 (1)	4 (4)	4 (4)	0 (0)	0 (0)
Lung infection	9 (8)	0 (0)	1 (1)	8 (7)	0 (0)	0 (0)
Pain	9 (8)	7 (6)	0 (0)	2 (2)	0 (0)	0 (0)
Upper respiratory tract infection	9 (8)	0 (0)	9 (8)	0 (0)	0 (0)	0 (0)

Urinary tract infection	9 (8)	1 (1)	3 (3)	5 (5)	0 (0)	0 (0)
Acute kidney injury	8 (7)	2 (2)	1 (1)	3 (3)	2 (2)	0 (0)
Herpes zoster	8 (7)	1 (1)	6 (6)	1 (1)	0 (0)	0 (0)
Memory impairment	8 (7)	7 (6)	1 (1)	0 (0)	0 (0)	0 (0)
Neck pain	8 (7)	7 (6)	1 (1)	0 (0)	0 (0)	0 (0)
Oropharyngeal pain	8 (7)	6 (6)	1 (1)	1 (1)	0 (0)	0 (0)
Pulmonary oedema	8 (7)	2 (2)	4 (4)	2 (2)	0 (0)	0 (0)
Urinary incontinence	8 (7)	3 (3)	4 (4)	1 (1)	0 (0)	0 (0)
Abdominal distension	7 (6)	6 (6)	1 (1)	0 (0)	0 (0)	0 (0)
Dysgeusia	7 (6)	6 (6)	1 (1)	0 (0)	0 (0)	0 (0)
Fall	7 (6)	4 (4)	3 (3)	0 (0)	0 (0)	0 (0)
Hiccups	7 (6)	4 (4)	3 (3)	0 (0)	0 (0)	0 (0)
Hyperkalaemia	7 (6)	5 (5)	2 (2)	0 (0)	0 (0)	0 (0)
Mental status changes	7 (6)	1 (1)	3 (3)	3 (3)	0 (0)	0 (0)
Non-cardiac chest pain	7 (6)	6 (6)	1 (1)	0 (0)	0 (0)	0 (0)
Pruritus	7 (6)	4 (4)	3 (3)	0 (0)	0 (0)	0 (0)
Sinus bradycardia	7 (6)	7 (6)	0 (0)	0 (0)	0 (0)	0 (0)
Sinusitis	7 (6)	2 (2)	5 (5)	0 (0)	0 (0)	0 (0)
Upper-airway cough syndrome	7 (6)	6 (6)	1 (1)	0 (0)	0 (0)	0 (0)
Atrial flutter	6 (6)	4 (4)	1 (1)	0 (0)	1 (1)	0 (0)
Blood creatinine increased	6 (6)	4 (4)	1 (1)	1 (1)	0 (0)	0 (0)
Dysuria	6 (6)	5 (5)	1 (1)	0 (0)	0 (0)	0 (0)
Nasal congestion	6 (6)	5 (5)	1 (1)	0 (0)	0 (0)	0 (0)
Ventricular arrhythmia	6 (6)	6 (6)	0 (0)	0 (0)	0 (0)	0 (0)
B-cell lymphoma	5 (5)	0 (0)	0 (0)	0 (0)	0 (0)	5 (5)
Blood alkaline phosphatase increased	5 (5)	4 (4)	0 (0)	1 (1)	0 (0)	0 (0)
Blood bilirubin increased	5 (5)	3 (3)	1 (1)	1 (1)	0 (0)	0 (0)
Clostridium difficile infection	5 (5)	0 (0)	3 (3)	2 (2)	0 (0)	0 (0)
Dysarthria	5 (5)	2 (2)	1 (1)	2 (2)	0 (0)	0 (0)
Dysphagia	5 (5)	2 (2)	3 (3)	0 (0)	0 (0)	0 (0)
Hallucination	5 (5)	3 (3)	2 (2)	0 (0)	0 (0)	0 (0)
Metabolic acidosis	5 (5)	3 (3)	0 (0)	2 (2)	0 (0)	0 (0)
Musculoskeletal pain	5 (5)	3 (3)	2 (2)	0 (0)	0 (0)	0 (0)
Peripheral swelling	5 (5)	3 (3)	2 (2)	0 (0)	0 (0)	0 (0)
Rash	5 (5)	4 (4)	1 (1)	0 (0)	0 (0)	0 (0)
Vision blurred	5 (5)	4 (4)	1 (1)	0 (0)	0 (0)	0 (0)
Weight increased	5 (5)	2 (2)	3 (3)	0 (0)	0 (0)	0 (0)
Ataxia	4 (4)	1 (1)	2 (2)	1 (1)	0 (0)	0 (0)
Atelectasis	4 (4)	4 (4)	0 (0)	0 (0)	0 (0)	0 (0)
Cardiac arrest	4 (4)	0 (0)	0 (0)	0 (0)	4 (4)	0 (0)
Clostridium difficile colitis	4 (4)	1 (1)	0 (0)	3 (3)	0 (0)	0 (0)
Dyspepsia	4 (4)	3 (3)	1 (1)	0 (0)	0 (0)	0 (0)
Ejection fraction decreased	4 (4)	0 (0)	2 (2)	2 (2)	0 (0)	0 (0)
Flatulence	4 (4)	1 (1)	3 (3)	0 (0)	0 (0)	0 (0)
Haematuria	4 (4)	3 (3)	1 (1)	0 (0)	0 (0)	0 (0)
Infusion related reaction	4 (4)	3 (3)	1 (1)	0 (0)	0 (0)	0 (0)
Malaise	4 (4)	2 (2)	2 (2)	0 (0)	0 (0)	0 (0)
Malnutrition	4 (4)	0 (0)	4 (4)	0 (0)	0 (0)	0 (0)
Rash maculo-papular	4 (4)	3 (3)	1 (1)	0 (0)	0 (0)	0 (0)
Restlessness	4 (4)	0 (0)	2 (2)	2 (2)	0 (0)	0 (0)
Seizure	4 (4)	0 (0)	3 (3)	0 (0)	1 (1)	0 (0)
Urinary retention	4 (4)	2 (2)	2 (2)	0 (0)	0 (0)	0 (0)
Wheezing	4 (4)	3 (3)	1 (1)	0 (0)	0 (0)	0 (0)
Abdominal discomfort	3 (3)	3 (3)	0 (0)	0 (0)	0 (0)	0 (0)
Abdominal pain upper	3 (3)	3 (3)	0 (0)	0 (0)	0 (0)	0 (0)
Ascites	3 (3)	1 (1)	0 (0)	2 (2)	0 (0)	0 (0)
Bone pain	3 (3)	2 (2)	0 (0)	1 (1)	0 (0)	0 (0)
Capillary leak syndrome	3 (3)	0 (0)	3 (3)	0 (0)	0 (0)	0 (0)
Chest discomfort	3 (3)	3 (3)	0 (0)	0 (0)	0 (0)	0 (0)
Deep vein thrombosis	3 (3)	0 (0)	3 (3)	0 (0)	0 (0)	0 (0)
Delirium	3 (3)	0 (0)	0 (0)	3 (3)	0 (0)	0 (0)
Disturbance in attention	3 (3)	1 (1)	0 (0)	2 (2)	0 (0)	0 (0)
Flank pain	3 (3)	2 (2)	1 (1)	0 (0)	0 (0)	0 (0)
Fluid overload	3 (3)	2 (2)	1 (1)	0 (0)	0 (0)	0 (0)
Gait disturbance	3 (3)	2 (2)	1 (1)	0 (0)	0 (0)	0 (0)
Gastrooesophageal reflux disease	3 (3)	1 (1)	2 (2)	0 (0)	0 (0)	0 (0)
Generalised oedema	3 (3)	1 (1)	1 (1)	1 (1)	0 (0)	0 (0)
Haemorrhoids	3 (3)	3 (3)	0 (0)	0 (0)	0 (0)	0 (0)

Hypermagnesaemia	3 (3)	3 (3)	0 (0)	0 (0)	0 (0)	0 (0)
Hypoglycaemia	3 (3)	2 (2)	1 (1)	0 (0)	0 (0)	0 (0)
Lethargy	3 (3)	1 (1)	2 (2)	0 (0)	0 (0)	0 (0)
Oral herpes	3 (3)	0 (0)	1 (1)	2 (2)	0 (0)	0 (0)
Orthostatic hypotension	3 (3)	0 (0)	2 (2)	1 (1)	0 (0)	0 (0)
Pancytopenia	3 (3)	0 (0)	1 (1)	1 (1)	1 (1)	0 (0)
Pollakiuria	3 (3)	3 (3)	0 (0)	0 (0)	0 (0)	0 (0)
Presyncope	3 (3)	0 (0)	3 (3)	0 (0)	0 (0)	0 (0)
Procedural pain	3 (3)	3 (3)	0 (0)	0 (0)	0 (0)	0 (0)
Productive cough	3 (3)	2 (2)	1 (1)	0 (0)	0 (0)	0 (0)
Rectal haemorrhage	3 (3)	3 (3)	0 (0)	0 (0)	0 (0)	0 (0)
Rhinitis allergic	3 (3)	3 (3)	0 (0)	0 (0)	0 (0)	0 (0)
Skin abrasion	3 (3)	1 (1)	2 (2)	0 (0)	0 (0)	0 (0)
Speech disorder	3 (3)	1 (1)	0 (0)	2 (2)	0 (0)	0 (0)
Swelling	3 (3)	2 (2)	1 (1)	0 (0)	0 (0)	0 (0)
Tachypnoea	3 (3)	2 (2)	1 (1)	0 (0)	0 (0)	0 (0)
Thrombosis	3 (3)	1 (1)	2 (2)	0 (0)	0 (0)	0 (0)
Tumour pain	3 (3)	0 (0)	2 (2)	1 (1)	0 (0)	0 (0)
Ventricular tachycardia	3 (3)	0 (0)	3 (3)	0 (0)	0 (0)	0 (0)
Acute left ventricular failure	2 (2)	0 (0)	0 (0)	2 (2)	0 (0)	0 (0)
Alopecia	2 (2)	2 (2)	0 (0)	0 (0)	0 (0)	0 (0)
Anal incontinence	2 (2)	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)
Arrhythmia	2 (2)	0 (0)	1 (1)	1 (1)	0 (0)	0 (0)
Bacteraemia	2 (2)	0 (0)	0 (0)	2 (2)	0 (0)	0 (0)
Blood immunoglobulin G decreased	2 (2)	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)
Candida infection	2 (2)	0 (0)	2 (2)	0 (0)	0 (0)	0 (0)
Depressed level of consciousness	2 (2)	0 (0)	0 (0)	2 (2)	0 (0)	0 (0)
Depression	2 (2)	2 (2)	0 (0)	0 (0)	0 (0)	0 (0)
Disorientation	2 (2)	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)
Dry eye	2 (2)	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)
Dry skin	2 (2)	2 (2)	0 (0)	0 (0)	0 (0)	0 (0)
Dyscalculia	2 (2)	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)
Dysphonia	2 (2)	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)
Escherichia bacteraemia	2 (2)	0 (0)	0 (0)	2 (2)	0 (0)	0 (0)
Flushing	2 (2)	2 (2)	0 (0)	0 (0)	0 (0)	0 (0)
Gastritis	2 (2)	2 (2)	0 (0)	0 (0)	0 (0)	0 (0)
Hemiparesis	2 (2)	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)
Herpes simplex	2 (2)	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)
Hyperaesthesia	2 (2)	2 (2)	0 (0)	0 (0)	0 (0)	0 (0)
Hypercalcaemia	2 (2)	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)
Hyperhidrosis	2 (2)	2 (2)	0 (0)	0 (0)	0 (0)	0 (0)
Hypersensitivity	2 (2)	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)
Hyperuricaemia	2 (2)	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)
Influenza	2 (2)	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)
Lactic acidosis	2 (2)	0 (0)	0 (0)	1 (1)	1 (1)	0 (0)
Localised oedema	2 (2)	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)
Micturition urgency	2 (2)	2 (2)	0 (0)	0 (0)	0 (0)	0 (0)
Mucosal inflammation	2 (2)	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)
Muscle spasms	2 (2)	2 (2)	0 (0)	0 (0)	0 (0)	0 (0)
Myelodysplastic syndrome	2 (2)	0 (0)	0 (0)	0 (0)	2 (2)	0 (0)
Myoclonus	2 (2)	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)
Neuropathy peripheral	2 (2)	2 (2)	0 (0)	0 (0)	0 (0)	0 (0)
Oedema genital	2 (2)	0 (0)	2 (2)	0 (0)	0 (0)	0 (0)
Oliguria	2 (2)	0 (0)	0 (0)	2 (2)	0 (0)	0 (0)
Oral candidiasis	2 (2)	0 (0)	2 (2)	0 (0)	0 (0)	0 (0)
Pain of skin	2 (2)	2 (2)	0 (0)	0 (0)	0 (0)	0 (0)
Photophobia	2 (2)	2 (2)	0 (0)	0 (0)	0 (0)	0 (0)
Post herpetic neuralgia	2 (2)	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)
Pruritus generalised	2 (2)	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)
Rhinitis	2 (2)	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)
Rhinorrhoea	2 (2)	2 (2)	0 (0)	0 (0)	0 (0)	0 (0)
Serum ferritin increased	2 (2)	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)
Sinus congestion	2 (2)	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)
Supraventricular tachycardia	2 (2)	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)
Vaginal haemorrhage	2 (2)	2 (2)	0 (0)	0 (0)	0 (0)	0 (0)
Abdominal X-ray	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Abdominal hernia	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Abdominal pain lower	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)

Abnormal dreams	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Acidosis	1 (1)	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)
Acute respiratory failure	1 (1)	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)
Adjustment disorder	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Amenorrhoea	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Amnesia	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Aspiration	1 (1)	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)
Atrioventricular block	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Bacterial sepsis	1 (1)	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)
Basal cell carcinoma	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Blepharospasm	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Blood albumin decreased	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Blood magnesium decreased	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Blood urea increased	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Blood uric acid increased	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Bone marrow failure	1 (1)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)
Bradycardia	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Bradyphrenia	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Brain injury	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)
Breath sounds abnormal	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Bronchitis	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Bronchopulmonary aspergillosis	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Bundle branch block right	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
C-reactive protein increased	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Carcinoma in situ	1 (1)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)
Cardiomegaly	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Catheter site haematoma	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Catheter site pain	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Catheter site swelling	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Cellulitis	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Cerebellar infarction	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Chapped lips	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Chest pain	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Coagulopathy	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Cognitive disorder	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Colitis	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Conjunctivitis	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Contusion	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Coordination abnormal	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Cytomegalovirus enteritis	1 (1)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)
Cytomegalovirus infection	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Cytomegalovirus viraemia	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Delusion	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Device related infection	1 (1)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)
Device related sepsis	1 (1)	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)
Diastolic hypotension	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Disseminated intravascular coagulation	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Dyskinesia	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Dyspareunia	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Ear discomfort	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Ear pain	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Ecchymosis	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Electrocardiogram QT prolonged	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Embolism venous	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Enteritis	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Erectile dysfunction	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Erythema	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Excessive cerumen production	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Extrasystoles	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Eye disorder	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Eye pain	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Face injury	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Face oedema	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Facial paralysis	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Facial paresis	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Fungal skin infection	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Graft versus host disease in skin	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Groin pain	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)

Haematoma	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Haemoptysis	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Haemorrhage intracranial	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)
Head discomfort	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Head titubation	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Heart rate irregular	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Hepatic enzyme increased	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Hepatitis B reactivation	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Hernia	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Herpes zoster oticus	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Histiocytosis haematophagic	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)
Human herpesvirus 6 infection	1 (1)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)
Hyperalbuminaemia	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Hyperbilirubinaemia	1 (1)	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)
Hypernatraemia	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Hypersomnia	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Hypertriglyceridaemia	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Hypervolaemia	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Hypoacusis	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Hypoaesthesia	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Hypothermia	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Hypouricaemia	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Ileus	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Inappropriate antidiuretic hormone secretion	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Increased tendency to bruise	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Infusion site infection	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Keratitis	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Klebsiella infection	1 (1)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)
Laryngeal haemorrhage	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Leukoencephalopathy	1 (1)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)
Limb discomfort	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Lip dry	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Lip swelling	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Livedo reticularis	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Liver function test abnormal	1 (1)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)
Liver function test increased	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Localised infection	1 (1)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)
Loss of consciousness	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Meningism	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Metabolic alkalosis	1 (1)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)
Mood altered	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Mouth ulceration	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Muscle spasticity	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Musculoskeletal chest pain	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Nasal dryness	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Nasogastric output abnormal	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Nasopharyngitis	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Neck mass	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Neurogenic bowel	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Night sweats	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Nocturia	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Obstructive airways disorder	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Oedema	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Oesophageal fistula	1 (1)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)
Oesophageal pain	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Oral discomfort	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Orthopnoea	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Osteomyelitis	1 (1)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)
Oxygen saturation decreased	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Palpitations	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Papilloedema	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Papule	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Paraesthesia	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Parainfluenzae virus infection	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Paranoia	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Parvovirus infection	1 (1)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)
Pelvic pain	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Periorbital oedema	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)

Peripheral sensory neuropathy	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Photopsia	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Pneumonia klebsiella	1 (1)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)
Pneumonia staphylococcal	1 (1)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)
Pneumothorax	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Polyuria	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Procedural headache	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Proctalgia	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Prothrombin time prolonged	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Psychomotor hyperactivity	1 (1)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)
Pulmonary congestion	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Pulmonary embolism	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)
Pulmonary haemorrhage	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Pulmonary hypertension	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Pupils unequal	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Rales	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Rash erythematous	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Reexpansion pulmonary oedema	1 (1)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)
Renal impairment	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Respiratory distress	1 (1)	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)
Respiratory rate increased	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Respiratory tract infection viral	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Retention cyst	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Retinal tear	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Rhinovirus infection	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Salmonellosis	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Scleral haemorrhage	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Scrotal oedema	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Sepsis	1 (1)	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)
Shock	1 (1)	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)
Sinus pain	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Skin lesion	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Skin ulcer	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Splenic infarction	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Splenic vein thrombosis	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Squamous cell carcinoma	1 (1)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)
Sternal fracture	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Stupor	1 (1)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)
Supraventricular extrasystoles	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Syncope	1 (1)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)
Thrombocytosis	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Thrombosis in device	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Tinea versicolour	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Tongue disorder	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Tongue fungal infection	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Tonsillar hypertrophy	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Toothache	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Torticollis	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Transaminases increased	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Troponin I increased	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Troponin T increased	1 (1)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)
Troponin increased	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Tumour lysis syndrome	1 (1)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)
Urinary tract infection bacterial	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Urinary tract obstruction	1 (1)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)
Urine output decreased	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Vaginal discharge	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Vagus nerve disorder	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Viral upper respiratory tract infection	1 (1)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)
Vitreous floaters	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Vulvovaginal candidiasis	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Wound infection	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)

Table* 6. Serious adverse events beyond 12 months in patients with ongoing remission.

Patient	SAE Start Time Post Axi-cel Infusion (month)	Grade	SAE	Attribution
1	15·6	3	Mental status changes	Vasovagal episode in the context of hypovolemia unrelated to axi-cel
2	18·9	4	Myelodysplastic syndrome	Prior chemotherapy unrelated to axi-cel
3	19·3	3	Lung infection	Unrelated to axi-cel
4	15·5	3	*Escherichia* bacteremia	Unrelated to axi-cel
	20·7	3	Bacteremia	Unrelated to axi-cel

Axi-cel=axicabtagene ciloleucel. SAE=serious adverse event.
*The previous analysis allowed for a minimum of 12 months of follow-up for all patients with a data cutoff of August 11, 2017.[5]

***Table* 7. Treatment-emergent cytopenias from all 108 patients treated on phase 1 and phase 2.**

Treatment-emergent adverse event	Any Grade	Grade ≥3
Any cytopenia on study	100 (93)	93 (86)
Thrombocytopenia	67 (62)	43 (40)
Neutropenia	93 (86)	86 (80)
Anemia	73 (68)	49 (45)
Any cytopenia present on day 30 or beyond	59 (55)	41 (38)
Thrombocytopenia	44 (41)	26 (24)
Neutropenia	39 (36)	28 (26)
Anemia	31 (29)	11 (10)
Any cytopenia present on month 3 or beyond	37 (34)	18 (17)
Thrombocytopenia	19 (18)	8 (7)
Neutropenia	20 (19)	12 (11)
Anemia	19 (18)	3 (3)
Any prolonged cytopenia lasting ≥30 days*	49 (45)	32 (30)
Thrombocytopenia	36 (33)	20 (19)
Neutropenia	24 (22)	15 (14)
Anemia	22 (20)	3 (3)

Per the standard Medical Dictionary for Regulatory Activities queries, thrombocytopenia includes hematopoietic thrombocytopenia (narrow), and anemia includes hematopoietic erythropenia (broad). Neutropenia includes preferred terms febrile neutropenia, neutropenia, and neutrophil count decreased.
*Majority of these events lasting ≥30 days occurred within the first 3 months after axicabtagene ciloleucel therapy.

Figure S1. **Consort diagram for phases 1 and 2 of ZUMA-1.**
*The median duration from leukapheresis to axicabtagene ciloleucel infusion was 23 days (IQR, 21–28 days). The longer durations in the range were mainly due to either patients' condition or adverse events related to conditioning chemotherapy. All grade 5 adverse events have been previously reported.[5,6] †Axicabtagene ciloleucel–unrelated event of pulmonary embolism. ‡Axicabtagene ciloleucel-related events of hemophagocytic lymphohistiocytosis and cardiac arrest in the context of CRS, and axicabtagene ciloleucel–unrelated events of intracranial hemorrhage.

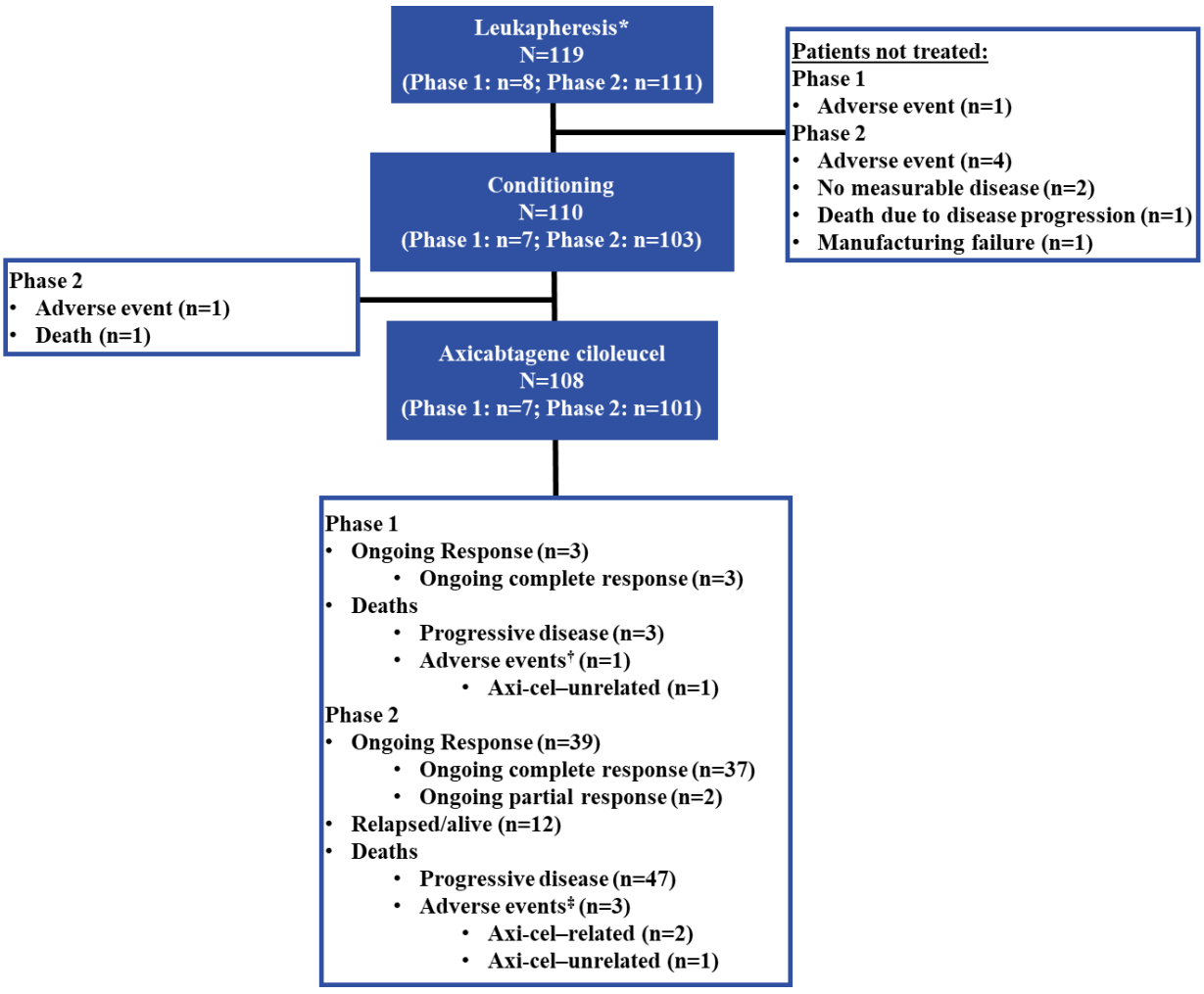


***Figure S2*. Time to objective response or complete response by investigator assessment among patients in phase 2 of ZUMA-1.**

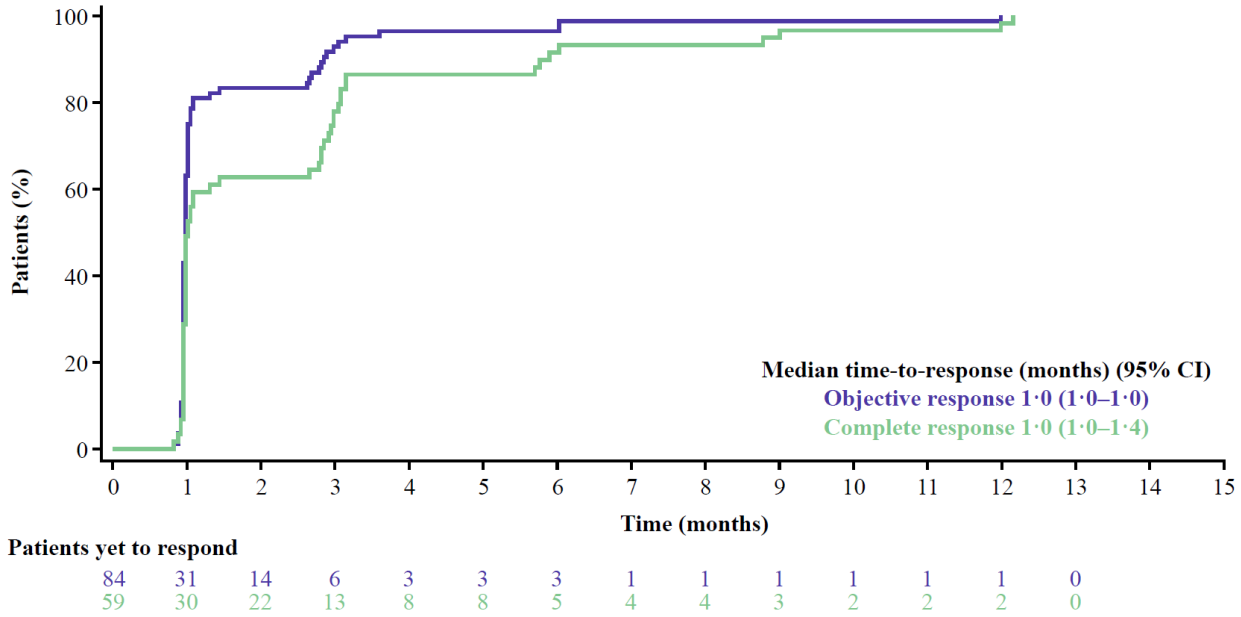


***Figure S3*. Duration of response by Independent Central Review Committee (IRC) review.**
Median duration of response was not reached (95% CI, 10·9 months – not estimable) by IRC review due to several patients with early progressive disease being assessed as in response by IRC review who had to be censored for receiving next anticancer therapy.

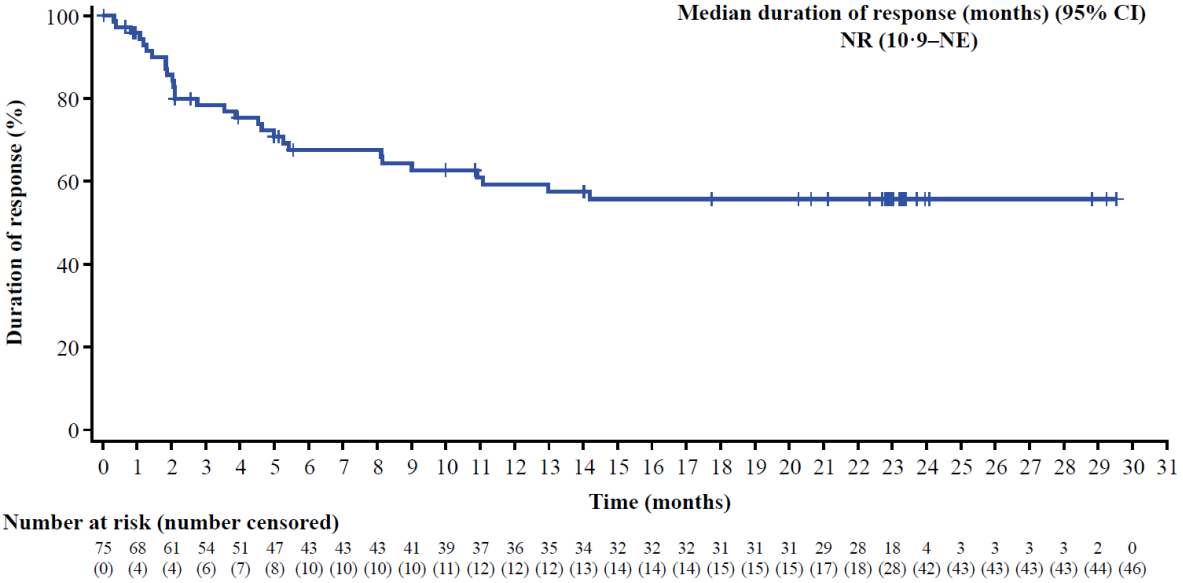


***Figure S4*. Subgroup analysis of ongoing responses at 24 months on phase 2 for subgroups with key baseline and clinical covariates.**

ASCT=autologous stem cell transplant. DLBCL=diffuse large B-cell lymphoma. ECOG=Eastern Cooperative Oncology Group performance status. IPI=International Prognostic Index. LCI=lower confidence interval. No.=number. PMBCL=primary mediastinal large B-cell lymphoma. TFL=transformed follicular lymphoma. UCI=upper confidence interval. *CD19 status was determined by histologic score for the 82 patients with available samples.

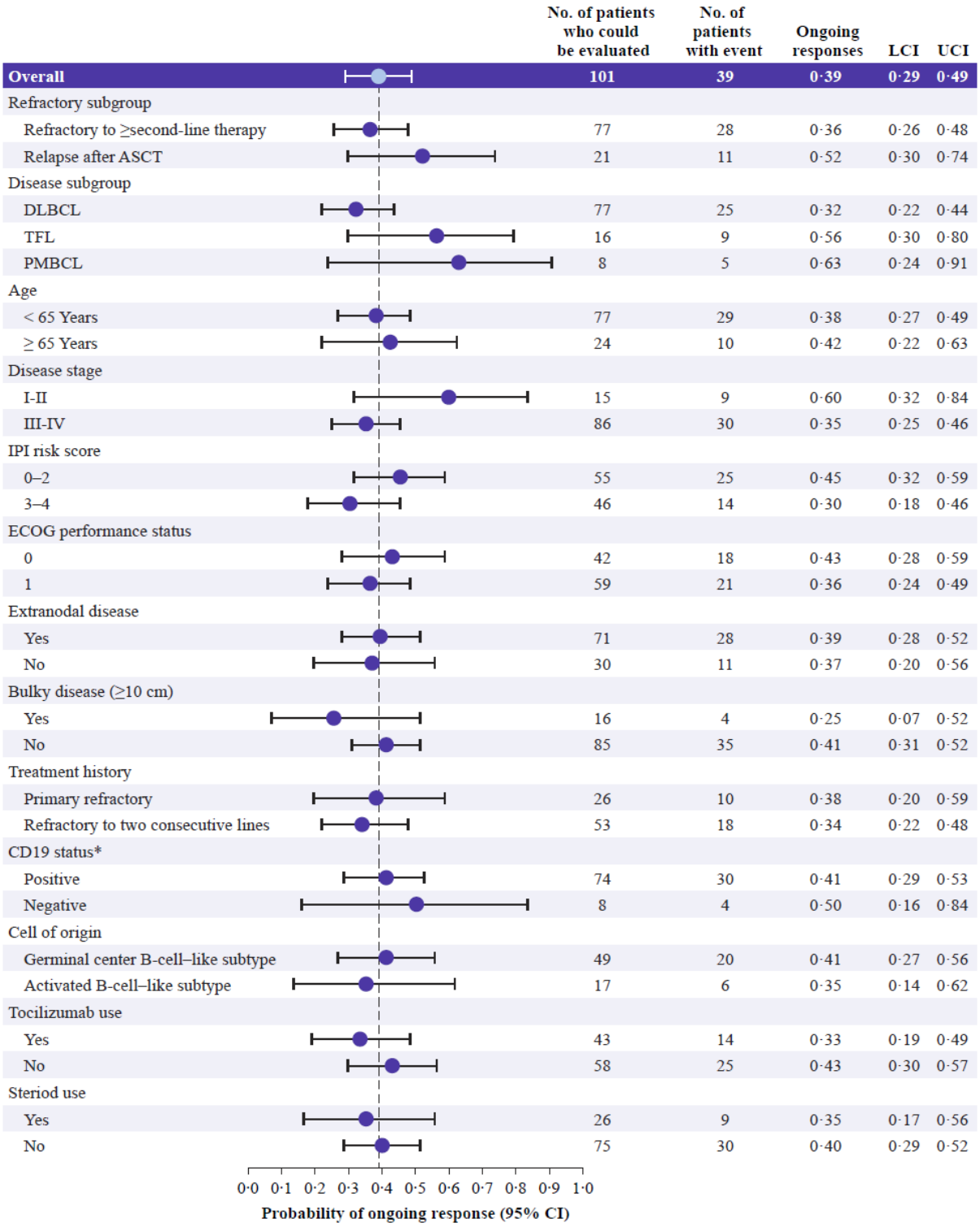
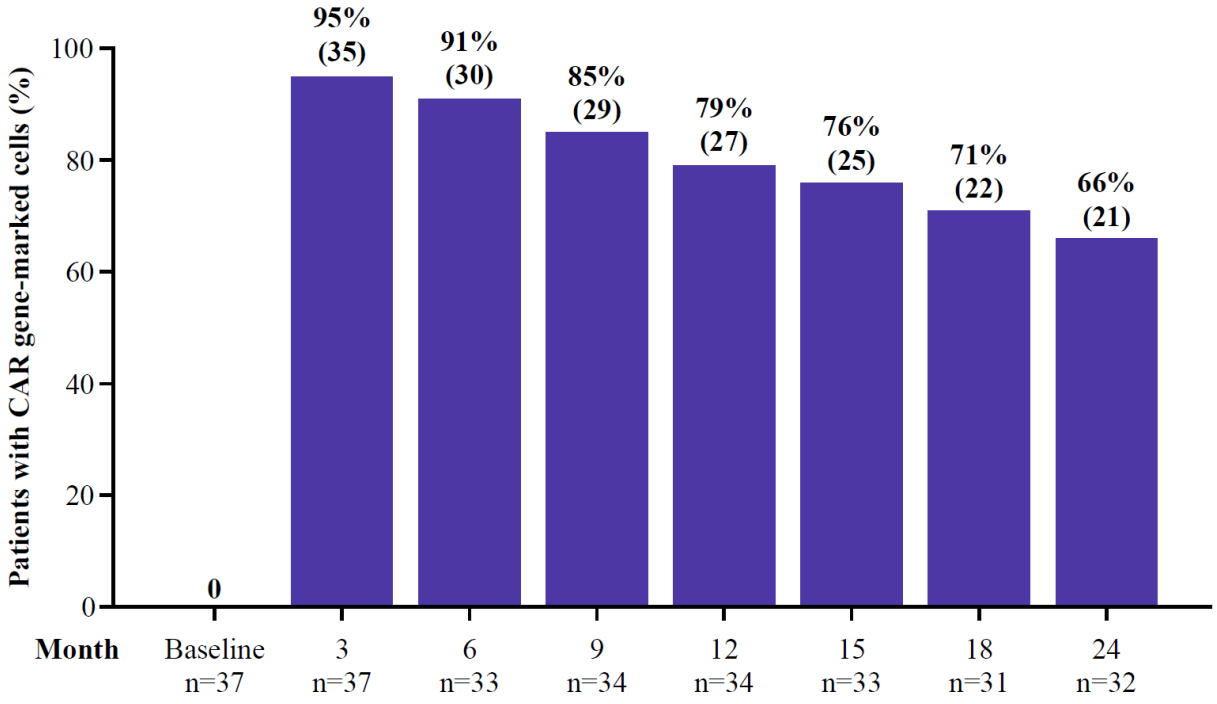


Figure S5. **Frequencies of patients with detectable CAR gene-marked cells within the subset of patients with ongoing response on phase 2.**

Gene-marked CAR T cells were enumerated by quantitative PCR. The lower limit of quantification of the assay was 2 gene-marked CAR T cells per 100,000 peripheral blood mononuclear cells (0.002%). Values shown indicate the proportion (top) and number (in parenthesis) of patients with gene-marked CAR T cells in blood at a given time point. Number of patients evaluated at each time point are shown on x-axis. This analysis excludes two patients who received subsequent anti-cancer therapy while in response to axi-cel. CAR=chimeric antigen receptor.



Supplemental References

1. Cheson BD, B. P, Juweid ME, et al. Revised response criteria for malignant lymphoma. *J Clin Oncol* 2007; **25**(5): 579-86.
2. Scott DW, Wright GW, Williams PM, et al. Determining cell-of-origin subtypes of diffuse large B-cell lymphoma using gene expression in formalin-fixed paraffin-embedded tissue. *Blood* 2014; **123**(8): 1214-7.
3. Swerdlow SH, Campo E, Pileri SA, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. *Blood* 2016; **127**(20): 2375-90.
4. Broyde A, Boycov O, Strenov Y, Okon E, Shpilberg O, Bairey O. Role and prognostic significance of the Ki-67 index in non-Hodgkin's lymphoma. *Am J Hematol* 2009; **84**(6): 338-43.
5. Neelapu SS, Locke FL, Bartlett NL, et al. Axicabtagene ciloleucel CAR T-cell therapy in refractory large B-cell lymphoma. *N Engl J Med* 2017; **377**(26): 2531-44.
6. Locke FL, Neelapu SS, Bartlett NL, et al. Phase 1 results of ZUMA-1: a multicenter study of KTE-C19 anti-CD19 CAR T cell therapy in refractory aggressive lymphoma. *Mol Ther* 2017; **25**(1): 285-95.

Statistical Analysis Plan and Protocol

This remainder of the appendix contains the following items:

1. Original statistical analysis plan (V1), final statistical analysis plan (V2), summary of changes
2. Original protocol (Amendment 1), final protocol (Amendment 5), summary of protocol changes.
    a. Note: The protocol has been redacted.

Sponsor:	Kite Pharma, Inc. 2225 Colorado Avenue Santa Monica, CA 90404 United States of America
Product Name:	KTE-C19
Version Number:	Version 1.0
Release Date:	
Replaces Previous Version:	Not applicable
Date:	**11 May 2015**

Table of Contents

1. Introduction

This statistical analysis plan provides the pre-specification and details for the statistical analyses outlined within protocol KTE-C19-101 entitled "A Phase 1-2 Multi-Center Study Evaluating the Safety and Efficacy of KTE-C19 in Subjects with Refractory Aggressive Non-Hodgkin Lymphoma (NHL)", dated 27 February 2015. The scope of this plan includes the interim, primary, and final analyses that are planned.

2. Objectives

The primary objective of phase 1 is to evaluate the safety of KTE-C19 regimens.

The primary objective of phase 2 is to evaluate the efficacy of KTE-C19, as measured by objective response rate in subjects with diffuse large B cell lymphoma (DLBCL), primary mediastinal B cell lymphoma (PMBCL), and transformed follicular lymphoma (TFL). Secondary objectives include assessing the safety and tolerability of KTE-C19 and additional efficacy endpoints as outlined below.

3. Study Overview

3.1 Study Design

Study KTE-C19-101 is a phase 1-2 multicenter, open-label study evaluating the safety and efficacy of KTE-C19 in subjects with refractory aggressive NHL. The trial will be separated into two distinct phases designated as phase 1 and phase 2.

For both phase 1 and phase 2, subjects will undergo

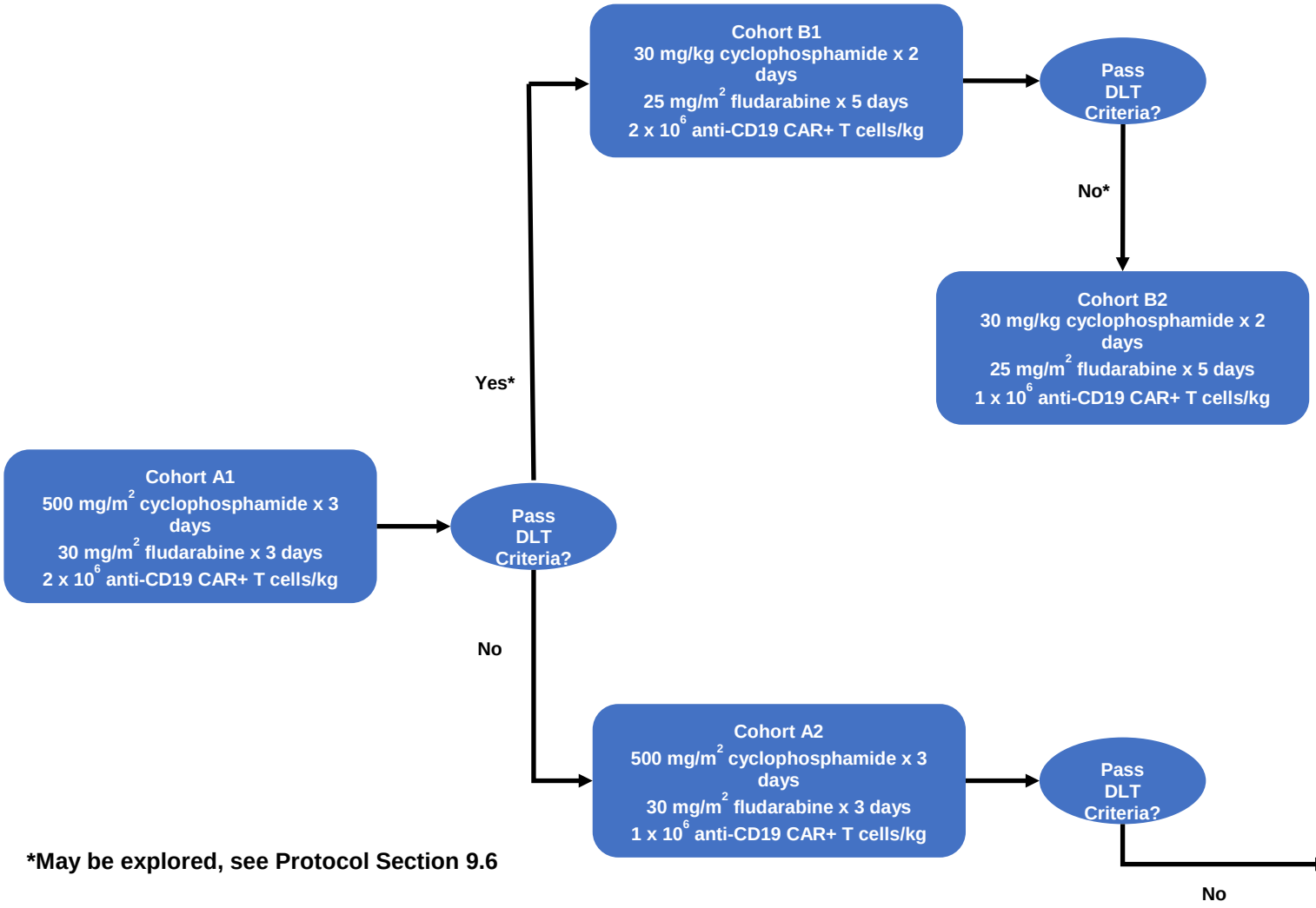
- Leukapharesis
- Conditioning chemotherapy treatment
- Investigational product treatment consisting of Chimeric Antigen Receptor (CAR) positive (+) T cells **(KTE-C19)**
- Post treatment assessment
- Long term follow-up

Further details on study procedures may be found in the study protocol.

During phase 1, approximately 6-24 subjects with refractory diffuse large B cell lymphoma (DLBCL), primary mediastinal B cell lymphoma (PMBCL), or transformed follicular lymphoma (TFL) will be enrolled to evaluate the safety of KTE-C19 regimens. If the initial regimen is determined to be safe, a higher dose of conditioning chemotherapy may be investigated. If the regimen is determined to not be safe, reduced doses of conditioning chemotherapy and/or KTE-C19 may be explored. A safety review team (SRT), internal to the study sponsor, will review the safety data and make

recommendations on further study conduct of phase 1 and progression to phase 2 as depicted in Figure 1 and outlined in Figure 3.

Figure 1. Phase 1 Dosing Cohorts and Regimens



***May be explored, see Protocol Section 9.6**

In phase 2, subjects will enroll into 2 separate cohorts designated as cohort 1 and cohort 2.

- Cohort 1 will enroll adult subjects with refractory DLBCL
- Cohort 2 will enroll adult subjects with refractory PMBCL and TFL

An independent data safety monitoring board (DSMB) will review safety and efficacy during the phase 2 portion of the study after 20 and 50 patients within cohort 1 have had the opportunity to complete the disease assessment at 3 months post KTE-C19 infusion. The primary analysis of efficacy endpoints will be based on investigator review of disease assessments and evaluated per the revised International Working Group Criteria for Malignant Lymphoma (Cheson, 2007), henceforth referred to throughout this document as "Investigator read - Cheson, 2007". Secondary efficacy analyses will be based on central radiologic review of disease assessments per Cheson, 2007; these assessments will be referred to throughout this document as "Central read – Cheson, 2007". The central radiologic review will also assess disease per Cheson, 2014; analyses based on this criteria will be described in a separate supplemental statistical analysis plan.

3.2 Hypothesis

This study is designed to differentiate between a treatment that has a true response rate of 20% or less and a treatment with a true response rate of 40% or more. The hypothesis is that the objective response rate to KTE-C19 in the DLBCL cohort and in the overall study population is significantly greater than 20%.

3.3 Sample Size Considerations

The anticipated enrollment in this study is approximately 118 to 136 subjects.

Six to 24 subjects will be enrolled into phase 1 of this study.

If the study proceeds to phase 2, approximately 72 subjects will be enrolled into cohort 1 and up to 40 subjects will be enrolled into cohort 2.

As indicated in section 3.1, KTE-C19 may be dosed at doses ranging from 1×10^6 to 2×10^6 mg/kg. The target dose of KTE-C19 for each cohort is provided in Table 1.

Table 1. Planned and Target Doses of KTE-C19

Cohort	Regimen and Planned Dose of KTE-C19	Target Dose of KTE-C19
A1	500 mg/m^2 cylcophosphamide x 3 days 30 mg/m^2 fludarabine x 3 days 2 x 10^6 anti-CD19 CAR+ T cells/kg	• 2 x 10^6 (+/- 20%) (1.6 x 10^6 up to and including 2.4 x 10^6) anti-CD19 CAR+ T cells/kg • For subjects weighing > 100 kg, a maximum flat dose of 2 x 10^8 anti-CD19 CAR + T cells
B1	30 mg/kg cyclophosphamide x 2 days 25 mg/m^2 fludarabine x 5 days 2 x 10^6 anti-CD19 CAR+ T cells/kg	• 2 x 10^6 (+/- 20%) (1.6 x 10^6 up to and including 2.4 x 10^6) anti-CD19 CAR+ T cells/kg • For subjects weighing > 100 kg, a maximum flat dose of 2 x 10^8 anti-CD19 CAR + T cells
B2	30 mg/kg cyclophosphamide x 2 days 25 mg/m^2 fludarabine x 5 days 1 x 10^6 anti-CD19 CAR+ T cells/kg	• 1 x 10^6 (+/- 20%) (0.8 x 10^6 up to and including 1.2 x 10^6) anti-CD19 CAR+ T cells/kg • For subjects weighing > 100 kg, a maximum flat dose of 1 x 10^8 anti-CD19 CAR + T cells
A2	500 mg/m^2 cylcophosphamide x 3 days 30 mg/m^2 fludarabine x 3 days 1 x 10^6 anti-CD19 CAR+ T cells/kg	• 1 x 10^6 (+/- 20%) (0.8 x 10^6 up to and including 1.2 x 10^6) anti-CD19 CAR+ T cells/kg • For subjects weighing > 100 kg, a maximum flat dose of 1 x 10^8 anti-CD19 CAR + T cells
A3	300 mg/m^2 cylcophosphamide x 3 days 30 mg/m^2 fludarabine x 3 days 2 x 10^6 anti-CD19 CAR+ T cells/kg	• 2 x 10^6 (+/- 20%) (1.6 x 10^6 up to and including 2.4 x 10^6) anti-CD19 CAR+ T cells/kg • For subjects weighing > 100 kg, a maximum flat dose of 2 x 10^8 anti-CD19 CAR + T cells

Efficacy analyses will be based on a modified intent to treat (mITT) population consisting of all subjects enrolled in the phase 2 portion of the study who receive the target dose of KTE-C19.

Safety analyses will be based on all subjects dosed with KTE-C19.

DLT analyses will be based on the DLT evaluable set, defined in Section 6.6.

This study uses a single arm design to test for an improvement in response rate in the DLBCL cohort (approximately n=72) and in the overall study population (cohorts 1 and 2 combined; n=112). For the test of efficacy, this study has ≥ 90% power to distinguish between an active therapy with a 40% true response rate from a therapy with a response rate of 20% or less with a 1-sided alpha of 0.025.

The overall 1-sided alpha level of 0.025 will be divided between the inference on cohort 1 and the inference in the overall study population using the methodology described in Song, 2007 and Wang, 2007. Using this methodology, the objective response rate for cohort 1 will be tested at a 1-sided alpha level of 0.022 and the objective response rate in the overall study population will be tested at a 1-sided alpha level of 0.0075. The derivation of these alpha levels is provided in Appendix 1.

Within cohort 1, 2 interim and 1 primary analyses will be performed.

- Interim analysis 1 will be conducted after 20 subjects in the mITT set have had the opportunity to be evaluated for response 3 months after the KTE-C19 infusion. This interim analysis will be for futility only.
- Interim analysis 2 will be conducted after 50 subjects have had the opportunity to be evaluated for response 3 months after the KTE-C19 infusion. This interim analysis will assess early demonstration of efficacy.
- The primary analysis of cohort 1 will occur after all subjects in cohort 1 have had the opportunity to be assessed for response 6 months after the KTE-C19 infusion.

An alpha spending function will be used to allocate the alpha level between interim analysis 2 of cohort 1 and the primary analysis of cohort 1. Using the Lan-DeMets family of alpha spending functions with a Pocock boundary, the nominal 1-sided alpha used to test for efficacy at interim analysis 2 of cohort 1 is 0.017 and the nominal 1-sided alpha used to test for efficacy at the primary analysis is 0.011. At the primary analysis of cohort 1, a statistically significant improvement in response will be determined if 23 or more subjects respond.

Within the overall study population, 1 primary analysis will be performed when all subjects accrued to cohorts 1 and 2 have **had the opportunity to be** assessed for response at 6 months after the KTE-C19 infusion. This testing will be performed at a 1-sided alpha level of 0.0075. For the targeted enrollment of 112 subjects in the overall study population **mITT set** (72 subjects in cohort 1 and up to 40 subjects in cohort 2), 34 or more responses must be observed in order to determine a statistically significant improvement in response. Confidence intervals about the objective response rates within cohorts 1 and 2 will be presented with the inferential analysis of the overall study population.

Enrollment of up to 40 subjects into cohort 2 is targeted, however, given the low prevalence of refractory PMBCL and TFL, fewer than 40 subjects may actually be enrolled. If at least 20 but fewer

than 40 subjects are accrued to the cohort 2 **mITT set**, the minimum number of subjects with response that must be observed in order to determine a statistically significant improvement in response ranges from 29 to 34 (Table 2). If less than 20 subjects are enrolled into cohort 2, the analysis of the overall study population will be descriptive and would occur no later than 2 years after completion of accrual into cohort 1. If the primary analysis of cohort 1 occurs prior to completion of accrual into cohort 2, inferential analyses of the overall study population will occur when 20 subjects have been accrued to the cohort 2 **mITT set**.

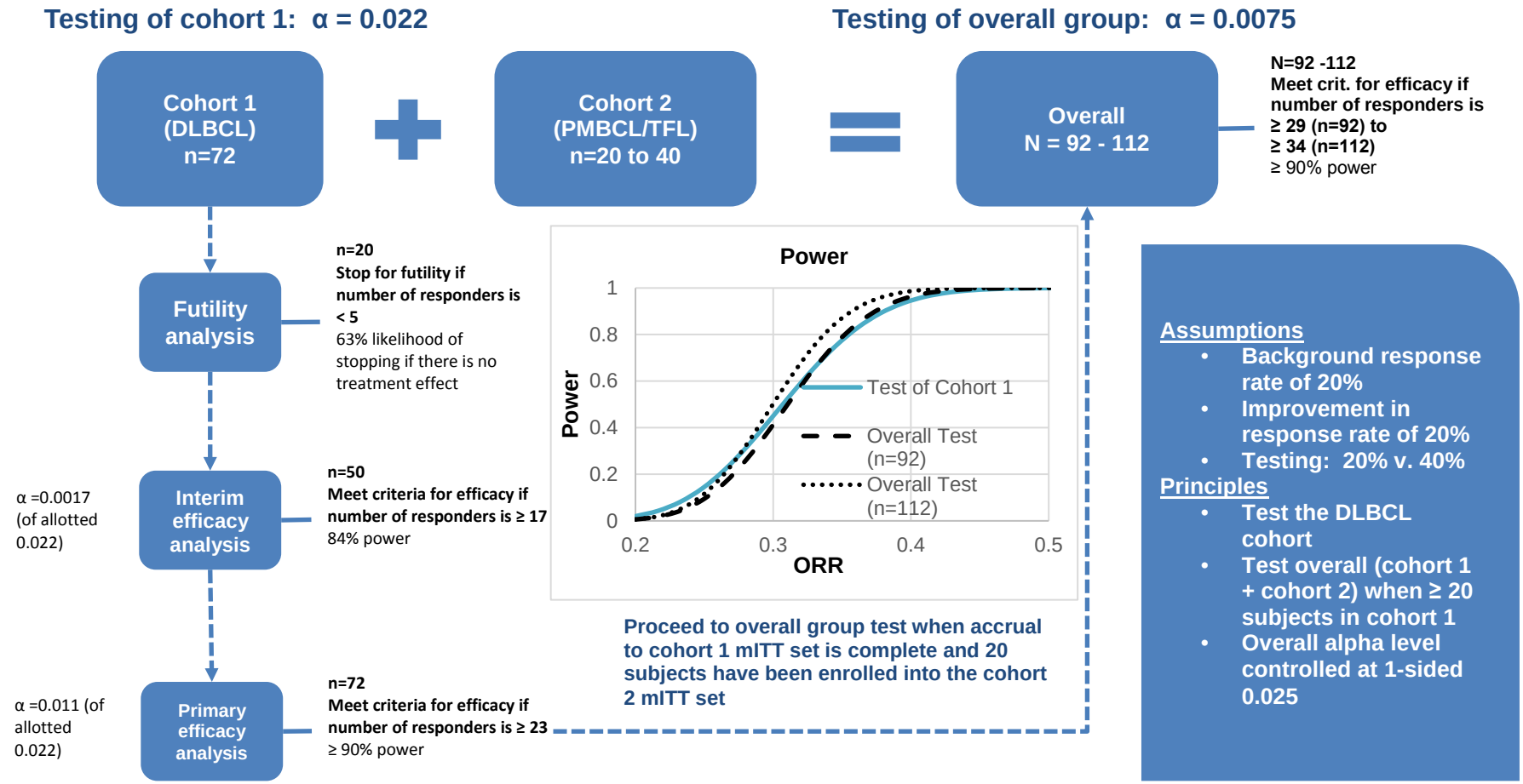
This procedure preserves the designated 1-sided alpha level of 0.025 and has ≥ 90% power. Simulation (10000 replicates) via R version 3.1.0 and EAST version 6.3 were used to evaluate the operating characteristics of this design.

A schema of the phase 2 study design is provided in Figure 2.

Table 2. Minimum number of responders required to determine statistical significance in the overall study population

Subjects enrolled in cohort 2	Subjects enrolled in study and in the mITT set for phase 2	Minimum number of responders required to determine statistical significance in the overall study population
20	92	29
21	93	29
22	94	30
23	95	30
24	96	30
25	97	30
26	98	31
27	99	31
28	100	31
29	101	31
30	102	32
31	103	32
32	104	32
33	105	32
34	106	33
35	107	33
36	108	33
37	109	33
38	110	34
39	111	34
40	112	34

Figure 2. Phase 2 Study Design Schema



3.4 Statistical Assumptions

This trial will enroll patients with chemo-refractory lymphoma, as evidenced by failure to achieve even a transient or partial response to prior biologic and combination chemotherapy or by early recurrence after ASCT.

Treatment outcomes for patients refractory to primary therapy or non-responsive to second line therapy are provided in Table 3 below. As indicated, the response to salvage therapy for these patients ranged from 0% to 26%. Based on these data, it is anticipated that the historical control for the objective response rate in the chemo-refractory population targeted in this study will be approximately 20%.

Table 3. Historical Responses in Refractory NHL (SD or PD to Last Line of Therapy)

Setting	Outcome to Subsequent Therapy
Refractory to 1st line	
Josting et al 2000 (n=64)	ORR 15%, median OS 6 mos
Phillip et al 1995 (n=28)	ORR 21%
Hitz et al 2010 (n=33)	Proceeded to ASCT 9%, 3% survived > 1 year
Ardeshna et al 2005 (n = 5)	ORR 0%
Telio et al 2012 (n = 111)	ORR 23%, median OS 10 mos
Matasar et al 2013 (n=10)	ORR 10%
Crump et al 2014 (n= 189)	ORR 26%
Refractory to 2nd line	
Moskowitz et al 1999 (n = 55)	Median OS 5 months
Ardeshna et al 2005 (n = 28)	ORR 18%, median OS (aggressive NHL) <6 mos
Seshadri et al 2008 (n=73)	ORR 14%
Relapsed post ASCT	
Nagle et al 2013 (N=45)	Median OS 8 months

This study assumes that the underlying response rate (in the absence of treatment with investigational therapy) is 20% and that an improvement in the response rate to 40% provides clinically meaningful benefit. In order to evaluate the validity of the assumption on the underlying response rate, retrospective studies (historical data and database reviews) of the response rate in the target population will be conducted.

4. Study Endpoints and Covariates

4.1 Endpoints

Primary (phase 1): the incidence of adverse events defined as DLTs

Primary (phase 2): the objective response rate (Investigator read - Cheson, 2007)

Secondary (phase 2**,** unless noted):

- Duration of response (Investigator read – Cheson, 2007)
- Best objective response (Investigator read - Cheson, 2007)
- Progression-free survival (Investigator read – Cheson, 2007)
- Overall survival
- Objective response rate (CR + PR) (Central read – Cheson, 2007)
- Duration of response (Central read – Cheson, 2007)
- Best objective response (Central read – Cheson, 2007)
- The incidence of adverse events
- The incidence of significant laboratory abnormalities
- The incidence and persistence of anti-KTE-C19 antibodies and anti-product impurity antibodies
- Levels and persistence of CAR+ T cells in serum samples
- Levels and persistence of cytokines in serum samples
- The subject incidence of replication competent retrovirus (RCR) detected in blood samples

Exploratory:

- Objective response rate (Investigator read - Cheson, 2007, Central read – Cheson, 2007) among subjects retreated with KTE-C19
- Duration of response (Investigator read – Cheson, 2007, Central read – Cheson, 2007) among subjects retreated with KTE-C19
- Change in tumor burden, as measured by baseline sum of the product of the diameters (SPD) of selected nodes or lesions to post-baseline nadir, per investigator measurements
- Change in tumor burden, as measured by baseline sum of the product of the diameters (SPD) of selected nodes or lesions to post-baseline nadir, per central read measurements
- The incidence of autologous stem cell transplant (ASCT) after treatment with KTE-C19
- Incidence and type of subsequent anti-cancer therapy
- Levels of lymphocyte subsets in blood samples

Endpoints related to product characterization (cell phenotypes in the KTE-C19 product, duration of cell manufacturing time, transduction ratios) and analyses related to these endpoints will be described in a supplemental statistical analysis plan.

4.2 Covariates

The following baseline covariates may be used to examine efficacy and / or safety in subgroups or covariate analyses:

- ECOG performance status at baseline
- Age at baseline (< 65, ≥ 65)
- Sex (male, female)
- Race: white, Asian, other (categories may be collapsed or expanded based on accrual)
- Disease type (DLBCL, PMBCL, TFL)
- Disease subtype (DLBCL associated with chronic inflammation, EPV + DLBCL, T cell / histiocyte rich large B cell lymphoma, DLBCL not otherwise specified, primary mediastinal (thymic) large B cell lymphoma, transformation of follicular lymphoma to DLBCL, other)
- Refractory subgroup (primary refractory (refractory to first line therapy), refractory to 2nd or greater line therapy, relapse post ASCT)
- Morphologic characteristics (centroblastic, immunoblastic, anaplastic, other)
- Molecular subgroup (germinal center B cell-like (GBC), activated B-cell like (ABC))
- BCL-2 alterations / overexpression (Y/N)
- BCL-6 alterations / overexpression (Y/N)
- C-MYC alterations / overexpression (Y/N)
- Double hit (C-MYC alterations or overexpression and either BCL-2 or BCL-6 alterations or overexpression) status
- Triple hit (BCL-2, BCL-6, and C-MYC alterations or overexpression) status
- Disease stage (I, II, III, IV) and extent (presence of B symptoms, bulky disease **(defined in Section 5.1)**, extranodal disease) at as determined by the investigator at screening
- International prognostics index (IPI) risk category at screening
- History of bone marrow involvement
- Number of prior chemotherapy regimens
- Prior therapy regimens (prior anti-CD20 (Y/N), prior anthracycline (Y/N), prior platinum (Y/N))
- Tumor burden, as measured by the SPD of selected nodes or lesions at baseline

Covariate levels that are sparse may be collapsed for purposes of statistical modeling.

5. Definitions

5.1 General

Study enrollment: Study enrollment occurs when a subject has consented for the study, completes the screening criteria, receives a subject identification number, **and is confirmed eligible for the study.**

Study day 1: Study day 1 is defined as the day the subject received the first KTE-C19 infusion. In the study protocol, the day of the first KTE-C19 infusion is referred to as study day 0, as this terminology is more familiar to investigative sites. However, in order to maintain consistency with CDISC data standards, the day of the first KTE-C19 infusion is defined as study day 1 for the purposes of this analysis plan and derived datasets. The day prior to study day 1 will be study day -1. Any days after enrollment and prior to study day -1 will be sequential and negative integer-valued. (see leukapharesis and conditioning chemotherapy period definitions)

Leukapharesis period: the leukapharesis study period is defined as the day (negative integer valued) the subject undergoes leukapheresis calculated relative to study day 1

Conditioning chemotherapy period: the conditioning chemotherapy period begins on the day of the first chemotherapy administration until the day immediately prior to the KTE-C19 infusion. These days are numbered as sequential negative integer values, and it is anticipated that these will be as follows for the various conditioning chemotherapy regimens:

- Cohorts A1, A2, A3: Day -5 through day -1 calculated relative to study day 1, with chemotherapy administered on days -5, -4, and -3.
- Cohorts B1, B2: Day – 7 through day -1 calculated relative to study day 1, with chemotherapy administered on days -7, -6, -5, -4, -3, -2, -1.

In the event that the KTE-C19 infusion is delayed, the numbering of the conditioning chemotherapy period will remain relative to the KTE-C19 infusion.

Retreatment conditioning chemotherapy period: the retreatment conditioning chemotherapy period begins on the day of the first chemotherapy administration of retreatment until the day immediately prior to the KTE-C19 retreatment infusion. In the event that the KTE-C19 retreatment infusion is delayed, the numbering of the retreatment conditioning chemotherapy period will remain relative to the KTE-C19 retreatment infusion.

Baseline: the baseline value is defined as the last value taken prior to conditioning chemotherapy

Study therapy: study therapy is defined as conditioning chemotherapy or KTE-C19

On-study: time from enrollment to the last date of contact

Long-term follow-up period: the long-term follow-up period begins the day after the post-treatment follow-up period up through and including the 15 year survival assessment.

End of study: This will occur after all subjects have been followed for 15 years post KTE-C19 infusion, have withdrawn consent, been lost to follow-up, experienced an adverse event that precluded further follow up, or have died.

Refractory Subgroup: Refractory subgroups are defined as below. A subject may meet the criteria for multiple refractory subgroups. In this event, the refractory subgroup defined by the subject's last line of therapy will be used to categorize the subject into a refractory subgroup.

- Primary refractory: A subject is considered to be primary refractory if the subject experienced disease progression as best response to first line therapy or had stable disease after at least 4 cycles of first line therapy with duration of stable disease no longer than 6 months from the last dose of therapy.
- Refractory to 2nd or greater line therapy: A subject is considered to be refractory to 2nd or greater line therapy if the patient experienced PD as best response to the most recent therapy regimen or experienced stable disease after at least 2 cycles of therapy with duration of stable disease no longer than 6 months
- Relapse post ASCT: A subject is considered to be relapsed post-ASCT if the subject experienced relapse ≤ 12 months of ASCT.

Bulky disease: bulky disease is defined as the presence of a single lesion with largest diameter 10 cm or larger or mediastinum wider than 1/3 of the chest on a chest x-ray. The presence of bulky disease will be determined by the investigator when baseline disease extent is evaluated.

5.2 Safety

Treatment-emergent adverse event (TEAE): any adverse event with onset on or after the first dose of conditioning chemotherapy up through and including the KTE-C19 treatment period, the primary post-treatment follow-up period, the secondary post treatment follow-up period, the KTE-C19 re-treatment period (if applicable), the primary post-treatment follow up period for re-treatment (if applicable), and the secondary post-treatment follow up period for retreatment (if applicable).

KTE-C19 Treatment Period: the KTE-C19 treatment period begins the day of the first KTE-C19 infusion up through and including 30 days after the KTE-C19 infusion.

KTE-C19 Re-treatment Period: the KTE-C19 re-treatment period begins the day of the re-treatment KTE-C19 infusion up through and including 30 days after the re-treatment KTE-C19 infusion.

Primary post-treatment follow-up period: the primary post treatment follow-up period begins the day after the KTE-C19 treatment period up through and including 92 days after the KTE-C19 infusion.

Secondary post-treatment follow-up period: the secondary post treatment follow-up period begins the day after the end of the primary post-treatment safety follow-up period and continues through disease progression or the end of the 15 year survival follow up, whichever occurs first.

Primary post-treatment follow-up period for re-treatment (defined only for subjects who undergo re-treatment with KTE-C19): the primary post-treatment follow up period for re-treatment begins the day after the KTE-C19 re-treatment period up through and including 92 days after the KTE-C19 retreatment infusion.

Secondary post-treatment follow-up period for re-treatment (defined only for subjects who undergo re-treatment with KTE-C19): the secondary post-treatment follow-up period for re-treatment begins the day after the primary post-treatment follow-up period for re-treatment and continues through disease progression after re-treatment or the end of the 15 year safety follow-up, whichever occurs first. This is the follow-up period over which targeted adverse events are collected.

Deaths through 30 days post KTE-C19 infusion: All deaths that occur from the beginning of the chemotherapy conditioning period up through the end of the KTE-C19 treatment period or occur from the beginning of the retreatment conditioning chemotherapy period up through the end of the KTE-C19 retreatment period.

Deaths through 92 days post KTE-C19 infusion: All deaths that occur from the beginning of the chemotherapy conditioning period up through the end of the primary post-treatment follow up period or occur from the beginning of the retreatment conditioning chemotherapy period up through the end of the primary post-treatment follow-up period for re-treatment

Deaths: All deaths that occur from the beginning of the chemotherapy conditioning period up through the end of study.

Fludarabine relative dose intensity: fludarabine relative dose intensity is the ratio of the actual cumulative dose of fludarabine to the cumulative protocol-specified dose of fludarabine for the conditioning chemotherapy period. For cohorts A1, A2, and A3, the cumulative protocol-specified dose of fludarabine is 90 mg/m^2. For cohorts B1 and B2, the cumulative protocol-specified dose of fludarabine is 125 mg/m^2.

Cyclophosphamide relative dose intensity: cyclophosphamide relative dose intensity is the ratio of the actual cumulative dose of cyclophosphamide to the cumulative protocol-specified dose of cyclophosphamide for the conditioning chemotherapy period. For cohorts A1 and A2 the

cumulative protocol-specified dose of cyclophosphamide is 1500 mg/m^2. For cohort A2, the cumulative protocol-specified dose of cyclophosphamide is 900 mg/m^2. For cohorts B1 and B2, the cumulative protocol-specified dose of cyclophosphamide is 60 mg/kg.

KTE-C19 relative dose intensity: KTE-C19 relative dose intensity is the ratio of the actual dose of KTE-C19 (CAR + cells/kg) to the planned dose of KTE-C19. The planned doses of KTE-C19 are provided in Table 1.

Adverse events of interest: Adverse events of interest for KTE-C19 treatment include adverse events in the categories of:

- Neurological toxicity
- Cytokine-release syndrome
- Hematological toxicity
- Infections
- Auto-immune disorders
- Secondary malignancies

Specific adverse events may be mapped these categories by dictionary coded event term. Specific definitions of these events and the coded terms to which they correspond will be provided in the Safety Monitoring Plan.

5.3 Efficacy

Objective Response Rate: proportion of subjects with either a CR or PR while on study. All subjects who do not meet the criteria for objective response by the analysis data cutoff date will be considered non-responders. The derivation of this endpoint will only include response assessments obtained after the initial KTE-C19 infusion and prior to any other additional therapy (e.g. stem cell transplant or retreatment with KTE-C19). Response may be defined per Investigator read - Cheson, 2007 or Central Read – Cheson, 2007.

Duration of response (DOR): DOR is defined only for subjects who experience an objective response and is the time from the first objective response to disease progression or **death due to disease relapse**. **Non-disease related mortality will be modeled as a competing risk.** Response and progression may be defined per Investigator read – Cheson, 2007 or Central Read – Cheson, 2007. Subjects not meeting the criteria for progression or death **due to disease relapse** by the analysis data cutoff date will be censored at their last evaluable disease assessment date. **DOR will be derived using disease assessments obtained on study prior to initiation of new anticancer therapy (excluding ASCT). Disease assessments obtained after ASCT will be used in the derivation of duration of response. A sensitivity analysis will be conducted in which disease assessments**

obtained after ASCT are not included in the derivation of DOR. Further details on the derivation of **DOR** are provided in Section 12.4.

Progression-free Survival (PFS): PFS is defined as the time from the KTE-C19 infusion date to the date of disease progression or death from any cause. Progression may be defined per Investigator read – Cheson, 2007 or Central Read – Cheson, 2007. Subjects not meeting the criteria for progression by the analysis data cutoff date will be censored at their last evaluable disease assessment date. **PFS will be derived using disease assessments obtained on study prior to initiation of new anti-cancer therapy (excluding ASCT). Disease assessments after ASCT will be used in the derivation of PFS.** Further details on the derivation of **PFS** are provided in Section 12.4.

Overall Survival (OS): OS is defined as the time from the KTE-C19 infusion to the date of death **from any cause**. Subjects who have not died by the analysis data cutoff date will be censored at their last contact date prior to the data cutoff date with the exception that subjects known to be alive or determined to have died after the data cutoff date for each analysis will be censored at the data cutoff date. Further details on the derivation of overall survival and the specific data modules that will be used to derive the last contact date are provided in Section 12.4.

Duration of response to retreatment (DORR): DORR is defined only for subjects who experience an objective response to retreatment and is the time from the first objective response after retreatment to disease progression after retreatment or **death due to disease relapse**. **Non-disease related mortality will be modeled as a competing risk.** Response and progression may be defined per Investigator read – Cheson, 2007 or Central Read – Cheson, 2007. Subjects not meeting the criteria for progression after retreatment or death **due to disease relapse** by the analysis data cutoff date will be censored at their last evaluable disease assessment date after retreatment. **DORR will be derived using disease assessments obtained on study prior to initiation of new anticancer therapy (excluding ASCT). Disease assessments obtained after ASCT will be used in the derivation of DORR. A sensitivity analysis may be conducted in which disease assessments obtained after ASCT are not included in the derivation of DORR.** Further details on the derivation of DORR are provided in Section 12.4.

6. Analysis Subsets

The following analysis sets are defined for each study phase separately.

6.1 Modified Intent-to-Treat (mITT)

The mITT analysis set will consist of all subjects enrolled and treated with the **target** dose of KTE-C19 in phase 2. This analysis set will be used for all efficacy analyses.

6.2 Safety Analysis Set

The safety analysis set is defined as all subjects treated with any dose of KTE-C19.

6.3 Full Analysis Set (FAS)

The FAS will consist of all enrolled patients and will be used for the summary of subject disposition, **sensitivity analyses of objective response rate and duration of response**, and subject listings of deaths.

6.4 mITT Re-treatment Analysis Set

The mITT Re-treatment Analysis Set will consist of the set of all subjects who undergo re-treatment with KTE-C19 at the **target** dose **administered in phase 2**. This set will be used for all re-treatment efficacy analyses.

6.5. Safety Re-treatment Analysis Set

The Safety Re-treatment Analysis Set will consist of all subjects who undergo re-treatment with KTE-C19.

6.5 Subgroup Analysis Sets

Subgroup analyses of selected efficacy and safety endpoints may be performed for the baseline covariates defined in Section 4.2

6.6 Interim Analysis Sets

The **DLT evaluable Set(s)** (phase 1 only), defined for each dosing cohort in phase 1, will include subjects treated in the phase 1 dosing cohort who:

- Received the target and were followed for at least 30 days after the KTE-C19 infusion; or
- Received a dose of anti-CD19 CAR+ T cells (KTE-C19) lower than the target for that cohort and experienced a DLT during the 30 day post-infusion period.

If needed, more subjects will be enrolled to achieve 6 DLT evaluable subjects at the target dose for each cohort.

The **Futility Analysis Set** will consist of the first 20 subjects **in** Cohort 1 (DLBCL) who meet the criteria for the mITT analysis set and who have had the opportunity to undergo a disease assessment 3 months after the KTE-C19 infusion.

The **Interim Analysis Set** will consist of the first 50 subjects **in** Cohort 1 (DLBCL) who meet the criteria for the mITT analysis set and who have had the opportunity to undergo a disease assessment 3 months after the KTE-C19 infusion.

7 Interim Analysis and Early Stopping Guidelines

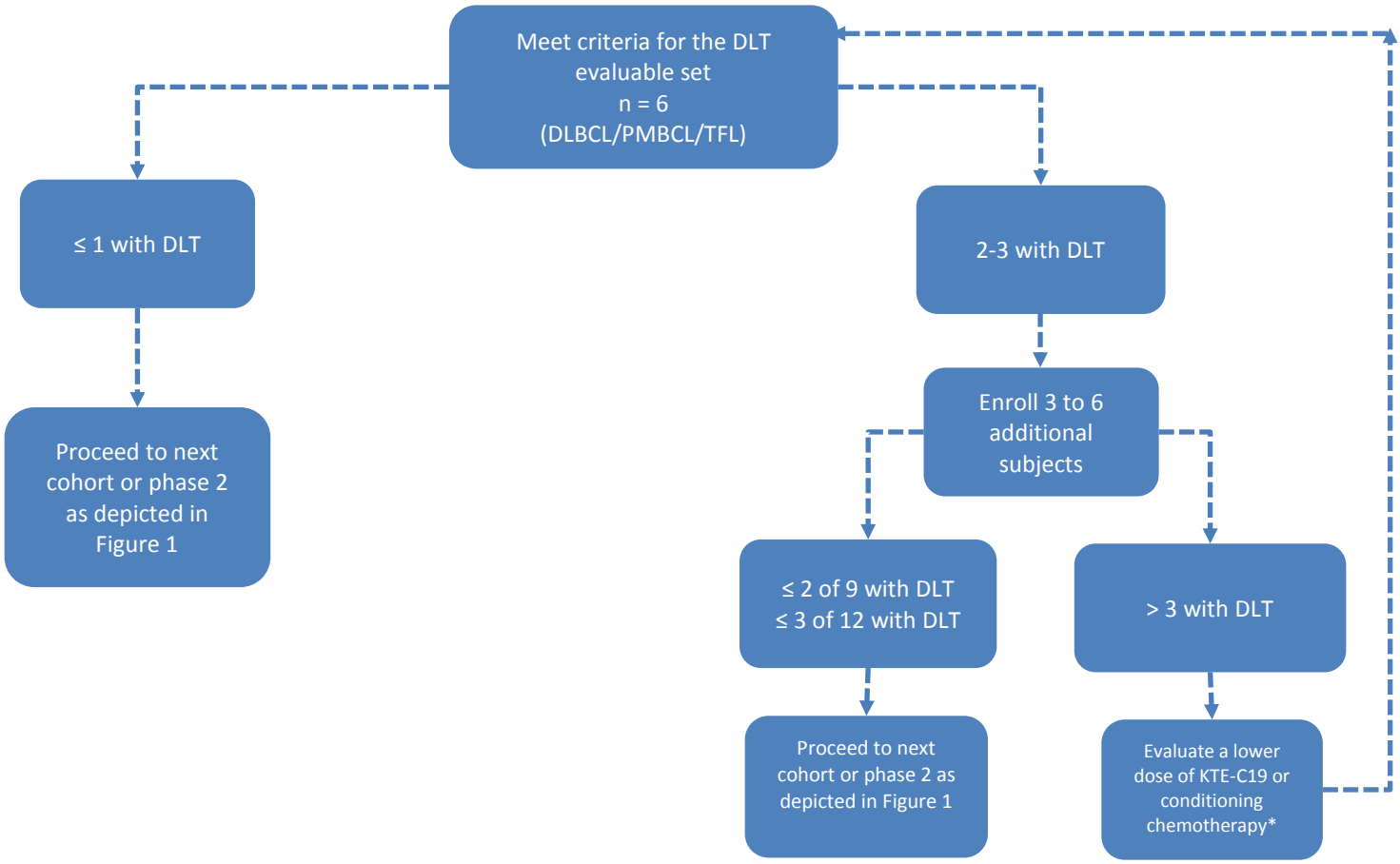
The SRT will review the safety data during phase 1 of the study and make a recommendation to progress the study from phase 1 to phase 2 based on the incidence of DLT and review of serious adverse events.

The DSMB will meet 2 times during the phase 2 portion of the study. The DSMB will review safety and efficacy data and will be chartered to make trial conduct recommendations based on the risk **versus** benefit of treatment with KTE-C19.

7.1 Phase 1 – Safety Interim Analyses

The SRT will evaluate the incidence of DLTs and serious adverse events after 6 subjects, 9 subjects (if applicable), and 12 subjects (if applicable) have met the criteria for the DLT evaluable set. The SRT may recommend **progression** to the phase 2 portion of the trial according to the schema in Figure 3.

Figure 3. Phase 1 DLT Evaluation Scheme



*or proceed to phase 2 with the dose previously tested in the NCI study, as depicted in Figure 1.

7.2 Phase 2 – Interim Safety and Efficacy Analyses

An independent DSMB will be chartered to make recommendations on study conduct during the phase 2 portion of the study. Details may be found in the Data Safety Monitoring Board Charter. The interim efficacy analyses will be conducted on subjects in Cohort 1 who meet the criteria for the Futility and Interim analysis sets. Safety analyses will present data from both study phases and both cohorts.

The first interim efficacy analysis will be conducted after 20 subjects in the Futility Analysis Set have had the opportunity to be followed for 3 months after the KTE-C19 infusion. This interim analysis will be for safety and futility. If more than or equal to 5 responses are observed in the first 20 subjects meeting the criteria for inclusion in this analysis, accrual to phase 2 will continue to the

planned 112 subjects. Otherwise, the DSMB may recommend a change to the study conduct. Under the null hypothesis, the likelihood of stopping for futility at this analysis is 63%.

The second interim efficacy analysis will be conducted after 50 subjects in the Interim Analysis set have had the opportunity to be followed for 3 months after the KTE-C19 infusion. This interim analysis will assess safety and early demonstration of efficacy. The nominal alpha level used for the conduct of this interim analysis is 0.017 (see Section 3.3). Using this boundary, the criteria for early efficacy may be met if 17 or more subjects respond. Under the alternative hypothesis, the likelihood of meeting the criteria for early efficacy at this interim analysis is 84%.

After the planned primary analysis of cohort 1 and the planned primary analysis of the study (cohorts 1 and 2 combined), additional efficacy and safety analyses may be performed to support regulatory interaction or publications. These analyses will be descriptive.

7.3 Access to Aggregate and Subject Level Data and Individual Subject Treatment Assignments

This study is open-label. Subjects, the study sponsor, and investigators will be aware that each subject is planned to be treated with KTE-C19. Data handling procedures designed to maintain the trial credibility and validity in this open-label single arm study are described in the Trial Integrity Document.

An independent statistician will perform the interim safety and efficacy analyses for the phase 2 portion of the study and provide these reports to the DSMB. Members of the DSMB and independent statistician will not have any direct contact with study center personnel or subjects. The DSMB will communicate recommendations to Kite Pharma in accordance with the DSMB charter.

8. Data Screening and Acceptance

8.1 General Principles

The database will be subject to the edit checks outlined in the Data Management Plan and additional manual data reviews defined by the study team. Data inconsistencies will be reviewed and resolved before the database snapshot for the primary analysis and the final database lock. For interim analyses, snapshots may include data that has not passed all data cleaning procedures at the time the data are extracted for snapshot.

8.2 Electronic Transfer and Archival of Data

The database for this study will be managed and maintained at Theorem Clinical Research. Datasets (raw data, SDTM data, and / or ADAM data) for planned analyses will be archived. Any additional

unplanned analyses that occur after the primary analysis and prior to the final analysis will also be archived. Key data external to the clinical study database (see below) will be included in the relevant SDTM and ADAM modules when the external data are available. For the SRT analyses, raw data may be archived and used in data review.

Data from the central pathology laboratory (tumor pathology, tumor genetic, and molecular characteristics), the product manufacture (total T cells, CAR + T cells (transduction ratio), duration of manufacturing time, central laboratory assessment of subject serum samples (CAR + T cell levels in the peripheral blood, antibody assays, RCR testing), and central radiology review will be generated from contract laboratories and Kite Pharma. These data will be transferred to Theorem Clinical Research and held in a peripheral directory and not built into the clinical trial database. At the time analyses require these data, they **may** be merged with the SDTM and ADAM datasets.

The source and disposition of all data sources obtained from imaging vendors or laboratories is described in Appendix 2.

8.3 Handling of Missing and Incomplete Data

8.3.1 Efficacy

The method for handling missing data is described in the definition for each efficacy endpoint. Every effort will be made to obtain complete dates for deaths. In the event of a partial or missing death date and the corresponding censoring date for survival, the algorithm in Section 12.2 will be used.

8.3.2 Safety

Partial adverse event start dates will be imputed. If dates are missing or incomplete for adverse event start dates, the algorithm defined in Section 12.2 will be used. Completely missing death dates or death dates with only a year reported will not be imputed.

8.4 Detection of Bias

A listing of subjects with important protocol deviations will be generated. The deviations included in this list will include violations of eligibility criteria and use of exclusionary medication during the study. Lack of protocol compliance will be evaluated by summarizing the subject incidence of important protocol deviations. High rates of important protocol deviations may indicate bias.

Endpoints derived from investigator assessment of radiologic scans and disease assessments may be subject to bias; the concordance between investigator and central review of radiologic scans and disease assessments will be summarized.

8.5 Outliers

Descriptive statistics will be used to identify potential outliers in any key variables analyzed. Suspected outliers may be evaluated with the generalized extreme Studentized deviate (EST) test conducted at a 0.01 significance level. Suspected outliers will be included in all analyses unless there is sufficient scientific justification to exclude them.

8.6 Distributional Characteristics

The primary analysis of the primary endpoint is an exact binomial test used to compare the observed response rate to a response rate of 20%. This test assumes only the independence of the individual subject responses. The validity of the assumption of a 20% historical response rate will be evaluated as described in Section 3.4.

An exact 95% confidence interval will be generated about the response rate. The Clopper-Pearson method will be used to generate this interval. While the Clopper-Pearson interval provides adequate coverage probability, it is commonly wider than necessary (Brown, 2002), leading to overly conservative estimates of the lower bound of objective response rate. Sensitivity analyses will be conducted in which the interval is calculated with different methods (Section 9.5.1).

8.7 Validation and Configuration Management

Programs for the development of the SDTM and ADAM datasets and the generation of the tables, figures, and listings will be developed and maintained according to Theorem Clinical Research Standard Operating Procedures. The software and version used to generate analyses will be indicated in the archived documentation.

9. Statistical Methods of Analysis

9.1 General Principles

The goal of the primary statistical analysis is to compare the observed response rate per investigator read - Cheson, 2007 to a historical control rate of 20% with an exact binomial test. Hypothesis testing will be one-sided, and all 95% confidence intervals will be 2–sided. At the time of the test of the overall study population, 95% confidence intervals for the response rate in each study cohort will be presented.

The timing of the interim and primary analyses will be based on subject accrual and disease assessment milestones. **The primary analysis clinical study report (CSR) will be written at the primary analysis of cohort 1. If the criteria for efficacy are met at the 50-subject interim analysis, the Kite Pharma may elect to write the CSR at the time of that analysis or may write the CSR at the**

time of the planned primary analysis. If the primary analysis CSR is written at the time of the interim efficacy analysis, it will be amended with the results of the planned primary analysis at the time the planned primary analysis is conducted. Additionally, the CSR will be amended with the analysis of the overall study population (including cohort 2) and may be amended with additional subject safety and survival follow up after the planned primary analysis.

Analyses of the phase 1 and phase 2 portions of the study will be presented separately. Within the phase 1 summaries, each dose cohort will be presented separately.

9.2 Subject Accountability

The number of subjects screened, enrolled, leukapheresed, treated with conditioning chemotherapy, treated with KTE-C19, and re-treated with KTE-C19 will be summarized. The reasons for discontinuing treatment and the disease assessment and survival follow-up periods will be summarized.

Summaries of actual and potential follow up time will be provided.

The number of subjects enrolled by country and site will be summarized.

The number of subjects in each analysis set along with reasons for exclusion will be provided.

9.3 Important Protocol Deviations

The clinical study team will define important protocol deviation categories and review all potential important protocol deviations at minimum, prior to the database snapshot for the primary efficacy analysis. Important protocol deviations will be categorized by deviation type (e.g. Entry/eligibility, use of excluded medication). The subject incidence of important protocol deviations will be summarized overall and by deviation category.

9.4 Demographic and Baseline Characteristics

Summary statistics and frequencies for the following demographic and baseline characteristics will be tabulated:

- ECOG performance status at baseline
- Sex (male, female)
- Weight
- Age at baseline (< 65, ≥ 65)
- Race: white, Asian, other (categories may be collapsed or expanded based on accrual)
- Disease type (DLBCL, PMBCL, TFL)

- Disease subtype (DLBCL associated with chronic inflammation, EBV + DLBCL, T cell / histiocyte rich large B cell lymphoma, primary cutaneous DLBCL (leg type), DLBCL not otherwise specified, primary mediastinal (thymic) large B cell lymphoma, transformation of follicular lymphoma to DLBCL, other)
- Number of prior chemotherapy regimens
- Response to last chemotherapy regimen (PD, SD) (among subjects who are not relapsed post ASCT)
- Refractory subgroup
- Prior autologous stem cell transplant (ASCT)
- Tumor burden, as measured by the SPD of selected nodes or lesions at baseline
- Morphologic characteristics (centroblastic, immunoblastic, anaplastic, other)
- Molecular subgroup (germinal center B cell-like (GBC), activated B-cell like (ABC))
- BCL-2 alterations / overexpression (Y/N)
- BCL-6 alterations / overexpression (Y/N)
- C-MYC alterations / overexpression (Y/N)
- Double hit (C-MYC alteration/overexpression and either BCL-2 or BCL-6 alteration/overexpression) status
- Triple hit (3 of 3 recurrent chromosome translocations) status
- Disease stage (I, II, III, IV) and extent (presence of B symptoms, bulky disease, extranodal disease)
- International prognostics index (IPI) risk category
- History of bone marrow involvement

  Disease pathology, genetic, and molecular characteristics will be evaluated by both the investigator and a central laboratory. The **central laboratory assessment** will be used in the primary statistical summaries.

9.5 Efficacy Analyses

Efficacy analyses will be conducted on the mITT analysis set. For the primary analysis, the investigator assessment of disease status per Cheson, 2007 will be used. Sensitivity analyses will be conducted that use the central radiology review of disease assessments per Cheson. The investigator and central radiology reviewer will provide the determination of disease status (CR, PR, SD, PD, NE) at each time point. SAS programs developed by Kite Pharma and Theorem Clinical Research will derive the best overall response, duration of response, and **progression-free survival** based on these assessments.

The primary efficacy analysis will be presented in the following subgroups:

- mITT set
- **FAS set (sensitivity analysis)**
- mITT set within the DLBCL cohort of the phase 2 portion of the study
- mITT set within the PMBCL / TFL cohort of the phase 2 portion of the study (descriptive analyses only)
- within each cohort of the phase 1 portion of the study, including all subjects in the cohort treated at the target dose who have the opportunity to be followed for at least one disease assessment

For subjects re-treated with KTE-C19, disease assessments obtained prior to retreatment but not disease assessment obtained after retreatment will be included in the primary summaries of objective and best response, duration of response, progression-free survival, and summaries of change in tumor burden. For such subjects, disease assessments obtained after re-treatment will be included in the summaries of objective and best response to retreatment with KTE-C19 and duration of response after re-treatment with KTE-C19. The subject's overall survival time will be derived from the last date known alive regardless of re-treatment time.

In the event any subject undergoes an autologous stem cell transplant (ASCT) or any additional anti-cancer therapy while on study, the subject's best response will be derived only based on disease outcomes assessed prior to ASCT or initiation of new therapy, whichever is earlier. For subjects without documentation of progression prior to initiation of new therapy (including ASCT), duration of response and progression-free survival time will be censored at the last disease assessment prior to the initiation of new therapy. A sensitivity analysis for progression-free survival may be conducted in which disease assessments after ASCT are used to derive events and censoring times. (Appendix 12.4).

9.5.1 Objective Response and Best Response

9.5.1.1 Primary Analyses of Objective Response

The subject incidence of objective response will be calculated. An exact binomial test will be used to compare the observed response rate to the hypothesized historical control rate of 20%. The subject incidence of best response (CR, PR, SD, PD, NE) will be calculated. Confidence intervals will be provided about the objective response rate and best response, calculated with the following methods:

- Clopper-Pearson (an exact interval)
- Wilson's method (sensitivity analysis)

- Agresti-Coull method (sensitivity analysis)
- The modified Jeffrey's method (Brown, 2001) (sensitivity analysis)

The primary analysis of objective response and best response will include subjects from the phase 2 portion and will be conducted for subjects in the DLBCL cohort (cohort 1) and the overall phase 2 study population (cohorts 1 and 2 combined). Descriptive summaries of the PMBCL/TFL cohort (cohort 2) will be provided with the inferential summary of the overall study population. **A sensitivity analysis of objective response will be conducted in the FAS set.**

9.5.1.2 Analyses of Objective Response and Best Response per Central Read

The analyses of objective response and best response specified above will be repeated for objective response and best response per central read – Cheson, 2007.

The concordance of objective response and best objective response per investigator read – Cheson 2007 and central read – Cheson 2007 will be evaluated. A summary table of concordance, concordance rate, a kappa statistic, and a 2-sided 95% confidence interval about the kappa statistic will be provided.

Further analyses between the investigator and central reads may be described in a supplemental SAP.

9.5.1.3 Subgroup Analyses of Objective Response

Objective response rates and 95% confidence intervals about response rates will be generated for subgroups of the mITT analysis set defined by:

- ECOG performance status at baseline
- Disease type
- Refractory subgroup
- Double hit status per central laboratory
- Triple hit status per central laboratory
- Disease stage and extent
- IPI risk category

A forest plot of the **proportion of responders** for each of these groups will be generated.

9.5.1.4 Analyses of Objective Response – Phase 1

Analyses of objective response in phase 1 may occur at any time during phase 1. The purpose of these analyses may include publications, preliminary evaluation of benefit-risk, and to inform decisions on dose.

At minimum, objective response rates and 95% confidence intervals will be generated for each dose cohort in phase 1.

9.5.2 Duration of Response

The competing-risk analysis method (Klein, 2005, Putter, 2007) will be used to estimate the cumulative incidence of relapse. The cumulative incidence of relapse in the presence non-disease related mortality (the competing risk) will be estimated along with 2-sided 95% confidence intervals at 3-monthly time intervals. **A plot of the cumulative incidence of relapse over time, and a stacked plot of the cumulative incidence of relapse and the cumulative incidence of death in the absence of relapse over time will be presented.** Additionally, multi-state time to event models may be used to estimate the hazard of death after relapse (illness-death model) and the hazard of relapse in the presence of non-disease related mortality (competing-risk model) (Putter, 2007). The number of subjects censored and the reasons for censoring will be summarized. Analyses will be generated for duration of response per investigator read – Cheson, 2007 and duration of response per central read – Cheson, 2007. **The reverse Kaplan-Meier approach (Schemper, 1996) will be used to estimate the follow up time for duration of response.**

A horizontal bar plot of each responding subject's duration of response, color coded for CR or PR status sorted by duration of response will be presented.

A sensitivity analysis of duration of response will be conducted in the FAS set.

A sensitivity analysis of duration of response will be conducted in which the duration of response for subjects undergoing ASCT is censored at the last evaluable disease assessment prior to ASCT.

9.5.3 Progression-free Survival

Kaplan-Meier plots, estimates and 2-sided 95% confidence intervals will be generated for progression-free survival. **Estimates of the proportion of subjects alive and progression-free at 3 month intervals will be provided.** The number of subjects censored and the reasons for censoring will be summarized. Analyses will be generated for progression-free survival per investigator read – Cheson, 2007 and progression-free survival per central read – Cheson, 2007.

The concordance of the assessment of progression per investigator read – Cheson 2007 and per central read – Cheson 2007 will be evaluated. A summary table of concordance (progression Y/N), concordance rate, a kappa statistic, and 2-sided 95% confidence interval about the kappa statistic will be provided. Summary statistics for the time difference between concordant assessments of progression will be provided.

Additionally, multi-state time to event models may be used to estimate the hazard of death after progression (illness-death model) (Putter, 2007).

9.5.4 Overall Survival

The analysis of overall survival will **use the same methods as the** analysis of progression-free survival **(with the exception of the concordance analysis between the investigator and radiology vendor)**. The reverse Kaplan-Meier approach (Schemper, 1996) will be used to estimate the follow up time for overall survival.

A graphical summary of the time to response, duration of response, retreatment, progression, and death times from the time of KTE-C19 infusion depicted on a horizontal time axis for each patient ("swim lane plot") will be provided.

9.5.5 Tumor Burden

The change in tumor burden, as measured by the sum of the products of the diameters of the selected lesions, from baseline to post-baseline nadir will be summarized in absolute numbers (mm^2) and percentage. A graphical summary of this change will be presented in a vertical bar chart with each subject's change from baseline to nadir displayed as a vertical bar, with color coding that indicates best response attained ("waterfall" plot). Summary statistics will be provided for this change. **Additionally, plots over time of the percent change in tumor burden for each subject (superimposed on one graph) will be presented.** Analyses will be generated for change in tumor burden per investigator read and per central read.

9.5.6 Objective Response and Best Response Among Subjects Re-treated with KTE-C19

The subject incidence of subjects re-treated with KTE-C19 will be tabulated. The subject incidence of objective response and best response (CR, PR, SD, PD, NE) **to the retreatment** among subjects re-treated with KTE-C19 will be calculated. Confidence intervals will be provided about the objective response rate and best response **to the retreatment**. Analyses may be conducted per investigator read – Cheson 2007 and central read – Cheson 2007.

9.5.7 Duration of Response Among Subjects Re-treated with KTE-C19

The analysis of duration of response **to retreatment** among subjects re-treated with KTE-C19 will **use the same methods** as the analysis of duration of response.

9.5.8 Incidence of ASCT

The subject incidence of ASCT post-treatment with KTE-C19 will be tabulated. Additionally, a sensitivity analysis of progression-free survival will be conducted in which disease assessments obtained after ASCT contribute to the progression-free time.

9.6 Safety Analyses

Safety analyses will be conducted on the safety analysis set. The primary analysis of safety data will summarize all treatment-emergent adverse events and laboratory values. Additional summary tables will present all treatment emergent adverse events, as well as adverse events with onset time categorized by study treatment period (conditioning chemotherapy treatment period, KTE-C19 treatment period, primary post-treatment follow up period, and secondary post-treatment follow up period). For subjects who undergo retreatment with KTE-C19, adverse events occurring in the KTE-C19 re-treatment period may be summarized in an additional separate summary that presents only the AEs occurring during the KTE-C19 retreatment period. Sample table layouts are provided in Appendix 3.

Adverse events will be coded with the Medical Dictionary for Regulatory Activities (MedDRA) at the time of each analysis. The version of the MedDRA may vary over time as the current version in use is updated. The severity of adverse events will be graded using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. Cytokine release syndrome (CRS) will be graded using a revised CRS grading scale developed by Lee et al (Lee, 2014) and per CTCAE 4.03. The incidence and severity of CRS will be reported as a syndrome with severity per Lee et al. Individual symptoms associated with CRS will be graded per CTCAE version 4.03.

Fatal adverse events that are attributed to disease progression will be summarized with a derived code of 'disease progression' regardless of the coded CTCAE version 4.03 preferred term.

Patients dosed with conditioning chemotherapy but not KTE-C19 will be followed for adverse events for 30 days after the first dose of conditioning chemotherapy. Adverse events reported in these patients will be archived in the study database and available in SDTM and ADAM datasets, but will not be tabulated in adverse event summaries.

Safety summaries will be presented separately for each phase 1 dosing cohort, for phase 2 cohort 1, phase 2 cohort 2, and phase 2 overall.

9.6.1 Adverse Events

The subject incidence of the following treatment-emergent adverse events will be tabulated for the:

- Summary of adverse events (any, worst severity, serious)
- All adverse events
- All serious adverse events
- **All leukapheresis-related adverse events**
- All conditioning-chemotherapy-related adverse events
- All KTE-C19-related adverse events
- All conditioning chemotherapy-related serious adverse events
- All KTE-C19-related serious adverse events
- All grade 3 or higher adverse events
- All grade 3 or higher conditioning chemotherapy-related adverse events
- All grade 3 or higher KTE-C19-related adverse events
- Fatal adverse events
- Adverse events of interest**,** including CRS events graded per Lee et al
- Dose limiting toxicity (phase 1 only, AEs with onset on or after the KTE-C19 infusion up through and including 30 days after the KTE-C19 infusion)

Summary statistics for the onset time (Kaplan-Meier estimates) and duration of adverse events of interest will be provided.

A subject listing of **deaths through 30 days post KTE-C19 infusion** and serious adverse events (including narratives) will be provided overall and by treatment period

A summary of demographics and baseline characteristics among subjects who experience CRS and who do not experience CRS will be provided.

9.6.2 Procedures and Concomitant Medications

The incidences of procedure and concomitant medications used to manage adverse events will be tabulated **(see Section 9.6.7).**

9.6.3. Laboratory Test Results

Laboratory results will be graded according to NCI Common Toxicity Criteria (CTCAE version 4.0**3**). Laboratory data collected at baseline and through the KTE-C19 Treatment Period will be summarized. Shifts from baseline to minimum post-baseline and / or maximum post-baseline will be presented for select analytes. The incidence of worst grade CTCAE shift for all analytes will be provided.

9.6.4 Anti-KTE-C19 antibodies

The subject incidence of any anti-KTE-C19 antibodies and anti-product impurity antibodies will be tabulated. For subjects testing positive for antibodies, the persistence of the antibody over time will be summarized.

9.6.5 Replication Competent Retrovirus (RCR)

The subject incidence of replication competent retrovirus (RCR) detected in blood samples will be tabulated overall and by assessment time. The persistence of RCR over time will be summarized.

9.6.6 Exposure to Study Treatment

Summary statistics for the number of infusions, cumulative BSA-adjusted dose of cyclophosphamide and fludarabine will be provided. Separate summaries will be presented for the 2nd administration of conditioning chemotherapy for subjects in the Re-treatment Analysis Set.

Summary statistics and a histogram of the total dose (10^6 CAR+ T cells/kg) of CAR + T cells, the total number of CAR + T cells, and the total number of T cells infused for the first KTE-C19 infusion will be provided. Separate summaries will be presented for the 2nd KTE-C19 infusion for subjects in the Re-treatment Analysis Set.

9.6.7 Exposure to Concomitant Medications and Procedures

The subject incidence of concomitant medications will be provided and summarized by medication category (general, gamma globulin, immunosuppressive, anti-infective, vaccinations, IV normal saline bolus, and vasopressor) and WHO Drug coded term. The subject incidence of procedures will be tabulated.

9.6.8 Mini Mental Status Exam (MMSE)

Summary statistics for the MMSE score and change from baseline in the MMSE score over time will be provided. A plot of the median change over time and 95% confidence interval bars will be provided.

9.7 Subsequent Anti-cancer Therapy

The incidence and type (by WHO Drug coded term and categories) of subsequent anti-cancer therapy will be summarized.

9.8 Schedule of Study Treatment

Summary statistics will be provided for the following durations:

- Days from leukapheresis to commencement of conditioning chemotherapy
- Days from leukapheresis to administration of KTE-C19
- Days from conditioning chemotherapy to administration of KTE-C19
- **Duration of hospitalization for the KTE-C19 infusion**

Separate summaries will be presented for the 2nd administration of study therapy for subjects in the Re-treatment Analysis Set.

9.9 CAR + T cells Measured in Peripheral Blood

Summary statistics for the level of CAR + T cells in serum post KTE-C19 infusion will be provided for CAR + T cells measured at day 7, week 2, week 4, month 3, month 6, month 12, and month 24. The maximum CAR+ T cell level attained, the time at which the maximum level was attained, and the time at which there were no detectable CAR + T cells in the serum will be summarized.

9.10 Lymphocyte Subsets

Summary statistics for the levels of lymphocytes and the subject incidence of **lymphopenia,** B-cell aplasia, and the subject incidence of recovery after **lymphopenia** and B-cell aplasia will be provided for each subject based on lymphocyte subsets measured prior to conditioning chemotherapy, on the day of the KTE-C19 infusion, week 4, month 3, month 6, month 9, month 12, month 15, month 18, and month 24. Graphical summaries of the median (Q1, Q3) value over time will be provided. Among subjects who experience **lymphopenia** or B-cell aplasia, summary statistics for the time to the onset of these conditions will be provided. The duration of **lymphopenia** and B-cell aplasia will be summarized; the duration of these events for subjects with persistent **lymphopenia** or B-cell aplasia at the last lymphocyte measurement will be censored at that time. **The use of IVIG treatment in the presence of B cell aplasia may be summarized.**

10. Changes from Protocol-Specified Analyses

The following changes have been made between this SAP and protocol version 1.0 (amendment #2), dated 27 February 2015.

- In the study protocol, the day of the KTE-C19 infusion is defined as day 0. In this statistical analysis plan, the day of the KTE-C19 infusion is defined as day 1. The rationale for this change is provided in Section 5.1.
- Additional exploratory endpoints have been added as described below:
    - Progression-free survival per central read – Cheson 2007
    - Changes in tumor burden per investigator assessment
    - Changes in tumor burden per central read

- Incidence of autologous stem cell transplant after treatment with KTE-C19
- Schedule of study treatment
- Incidence and type of subsequent anti-cancer therapy

The rationale for the addition of these endpoints is that these endpoints are useful to more thoroughly characterize the efficacy, safety, and logistical management of treatment with KTE-C19.

11. References

Ardeshna KM, Kakouros N, Qian W, et al. Conventional second-line salvage chemotherapy regimens are not warranted in patients with malignant lymphomas who have progressive disease after first-line salvage therapy regimens. *Br J Haematol.* 2005 Aug;130(3):363-72.

Brown SD, Cai TT, and DasGupta A. Interval Estimation for a Binomial Proportion. *Statistical Science.* 2001;16:101-133.

Brown LD, Cai TT, DasGupta A. Confidence Intervals for a Binomial Proportion and Asymptotic Expansions. *The Annals of Statistics.* 2002; 30:160-201.

Cheson BD, Pfistner B, Juweid ME, Gascoyne RD, Specht L, Horning SJ, et al. Revised response criteria for malignant lymphoma. *J Clin Oncol.* 2007;25(5):579

Cheson BD, Fisher RI, Barrington SF, Cavalli F, Schwartz LH, Zucca E, and Lister TA. Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification, *J Clin Oncol.* 2014.

Crump M, et al. Randomized Comparison of Gemcitabine, Dexamethasone, and Cisplatin Versus Dexamethasone, Cytarabine, and Cisplatin Chemotherapy Before Autologous Stem-Cell Transplantation for Relapsed and Refractory Aggressive Lymphomas: NCIC-CTG LY.12, *J Clin Oncol*., 2014; 32:3490-3496.

Hitz F, Connors JM, Gascoyne RD, Outcome of Patients with Chemotherapy Refractory and Early Progressive Diffuse Large B Cell Lymphoma After R-CHOP Treatment; *Blood* (ASH Annual Meeting Abstracts, Poster Session) 2010 116: Abstract 1751

Josting A, et al. Prognostic factors and treatment outcome in primary progressive Hodgkins Lymphoma: a report from the German Hodgkin study group; *Blood* 2000 August 15; 96: 1280-1286.

Klein JP, Moeschberger ML, Survival Analysis: Techniques for Censored and Truncated Data. Springer, 2005.

Lan-Demets/Pocock: KK Gordon Lan and David L. DeMets, Discrete sequential boundaries for clinical trials, I 983; 70:3:659-663.

Matasar MJ, Czuczman MS, Rodriguez MA, et al. Ofatumumab in combination with ICE or DHAP chemotherapy in relapsed or refractory intermediate grade B-cell lymphoma. *Blood.* 2013; 122(4):499-506

Nagle SJ, Woo K, Schuster SJ, Nasta SD, Stadtmauer E, Mick R and Svoboda J. Outcomes of patients with relapsed/refractory diffuse large B-cell lymphoma with progression of lymphoma after autologous stem cell transplantation in the rituximab era. *J Hematol*. 2013; 88:890-894.

Philip T, Guglielmi C, Hagenbeek A, et al. Autologous bone marrow transplantation as compared with salvage chemotherapy in relapses of chemotherapy-sensitive non-Hodgkin's lymphoma. *N Engl J Med.* 1995; 333: 1540-5.

Putter H, Tutorial in biostatistics: Competing risks and multi-state models. *Statistics in Medicine,* 2007; 26: 2389-2430.

Schemper M, Smith TL A note on quantifying follow-up in studies of failure time. *Control Clin Trials* 17: 343-346, 1996.

Seshadri T, Kuruvilla J, Crump M, Keating A. Salvage therapy for relapsed/refractory diffuse large B cell lymphoma. *Biol Blood Marrow Transplant.* 2008 Mar;14(3):259-67.

Song Y, Chi GYH. A method for testing a prespecified subgroup in clinical trials, *Statistics in Medicine*, 2007; 26:3535-3549

Telio D, Fernandes K, Ma C, et al. Salvage chemotherapy and autologous stem cell transplant in primary refractory diff use large B-cell lymphoma: outcomes and prognostic factors. *Leukemia & Lymphoma*. 2012; 53(5): 836-841.

Wang: Sue-Jane Wang, Approaches to evaluation of treatment effect in randomized clinical trials with genomic subset, *Pharmaceutical Statistics*, 2007; 6:227-244

12 Appendices

12.1 Appendix 1: Derivation of split alpha levels

The calculation of the split alpha levels is based on the methods in Song and Chi (2007) and Wang (2007) as follows:

- The overall alpha level is 1-sided α=0.025.
- Denote the alpha level for the test of the overall study population as α_1, with α_1=0.0075.
- The alpha level for the test of cohort 1 is denoted by α_2 and is obtained by solving the following equation for α_2:

$$\int_{-\infty}^{z_{\alpha_1}} \Phi\left(\frac{z_{\alpha_2} - \sqrt{p}\, z_1}{\sqrt{1-p}}\right) \phi(z_1) dz_1 = 1 - \alpha$$

Where $\phi(\cdot)$ is the normal density function, z_β is the normal upper 100β percentile, and p is the proportion of subjects in cohort 1 relative to the overall study population. Given that accrual to cohort 2 may range between 20 and 40 subjects, the value of α_2 obtained from the equation above when accrual to cohort 2 is 40 was used to prospectively define the split alpha levels. This value results in lower alpha levels and hence ensures control of the type I error.

12.2 Appendix 2: Source and Disposition of Non-Clinical Database Data

Sample Type	Analysis / Data Element	Testing Lab / Source	Responsible to transfer to TCR	Include in Clinical Data Submitted to FDA	Analysis Plan
Product cells	Total T cells	PCT / Batch record	Kite/TCR[a]	Yes	Primary SAP
Product cells	Transduction rate	PCT / Batch record	Kite/TCR[a]	Yes	Primary SAP
Product cells	% CAR + T cells	PCT / Batch record	Kite/TCR[a]	Yes	Primary SAP
Product cells	Days of manufacture	PCT / Batch record	Kite/TCR[a]	Yes	Primary SAP
Product cells	Cell differentiation and phenotype	Kite	Kite	No	Supplemental translational research SAP
Product cells	Cytokines (co culture)	Kite	Kite	No	Supplemental translational research SAP
Biospecimen (post KTE-C19 infusion samples)	Cell differentiation and phenotype	Kite	Kite	No	Supplemental translational research SAP
Biospecimen	Cytokines	Kite	Kite	No	Supplemental translational research SAP
Biospecimen	CAR PCR	URMC	URMC	Yes	Primary SAP and Supplemental translational research SAP
Biospecimen	Antibody	Alta Intertek	Alta	Yes	Primary SAP
Biospecimen	RCR	Remidion	Remidion	Yes	Primary SAP
Biospecimen	LAM PCR	TBD	TBD	Yes	Primary SAP
Tissue blocks	Paired biopsy	TBD	TBD	No	Supplemental SAP
Tissue blocks	Pathology	UCLA	UCLA	Yes	Primary SAP
Independent Radiology Review	Cheson 2007	Bioclinica	Bioclinica	Yes	Primary SAP
Independent Radiology Review	Cheson 2014	Bioclinica	Bioclinica	Yes	Supplemental Concordance SAP

[a] Data to be initially entered into a comma delimited file by QA staff from Kite. TCR will perform a QC check that the source documentation (pdf of the batch record) matches the electronic file.
In the event of a data entry error, TCR will correct the data file with the value in the batch record and notify Kite that the update has been made.

All data will be archived at TCR. Data indicated as 'Yes' for inclusion in the clinical data submitted to FDA will be merged with the clinical data. Data indicated as 'No' for inclusion in the clinical data submitted to FDA will be archived at TCR but not merged with the clinical data.

12.2 Appendix 2: Conventions for Clinical Data That Require Imputation for Partial or Missing Dates

The following data will be imputed using the following algorithm:

- Adverse event start dates
- Deaths (please see exceptions below)
- Concomitant medication start dates
- Subsequent anti-cancer therapy start dates

Table 2. Imputation Rules for Partial or Missing Start Dates

Start Date		Stop Date						
		Complete: *yyyymmdd*		Partial: *yyyymm*		Partial: *yyyy*		Missing
		< day 1	≥ day 1	< day 1 *yyyymm*	≥ day 1 *yyyymm*	< day 1 *yyyy*	≥ day 1 *yyyy*	
Partial *yyyymm*	= day 1 *yyyymm*	2	1	2	1	n/a	1	1
	≠ day 1 *yyyymm*		2		2	2	2	2
Partial *yyyy*	=1st dose *yyyy*	3	1	3	1	n/a	1	1
	≠ 1st dose *yyyy*		3		3	3	3	3
Missing		4	1	4	1	4	1	1

1 = impute the date of day 1
2 = impute the first of the month
3 = impute January 1 of the year
4 = impute January 1 of the stop year
Note: if the start date imputation leads to a start date that is after the stop date, then do not impute the start date.

Imputation rules for partial or missing death dates:

1. If death year and month are available but day is missing:
    - If mmyyyy for the last contact date = mmyyyy for death date, set death date to the day after the last contact date.
    - If mmyyyy for the last contact date < mmyyyy for death date, set death date to the first day of the death month.
    - If mmyyyy for last contact date > mmyyyy for death date, data error and do not impute.
2. If both month and day are missing for death date or a death date is completely missing, do not impute and censor the subject survival time at the last contact date.

12.3 Appendix 3: Sample Adverse Event Table Layouts

Sample Adverse Event Summary Layout 1: All AE summaries listed in Section 9.6.1 will be provided in format 1. The preferred terms will be sorted by descending order of frequency of the All, Any column.

Phase 1:

Subject Incidence of <AE Descriptor> Adverse Events in Descending Order of Preferred Term by Worst Severity: Phase 1

	Cohort A1				Cohort <B1 or A2 or not present>				Cohort <B2 or A3 or not present>			
	Any	Gr 3	Gr 4	Gr 5	Any	Gr 3	Gr 4	Gr 5	Any	Gr 3	Gr 4	Gr 5
Any <AE Descriptor> Adverse Event – n(%)	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)
Preferred Term 1	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)
Preferred Term 2	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)

Phase 2:

Subject Incidence of <AE Descriptor> Adverse Events in Descending Order of Preferred Term by Worst Severity

	Cohort 1: DLBCL				Cohort 2: PMBCL/TFL				All Phase 2			
	Any	Gr 3	Gr 4	Gr 5	Any	Gr 3	Gr 4	Gr 5	Any	Gr 3	Gr 4	Gr 5
Any <AE Descriptor> Adverse Event – n(%)	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)
Preferred Term 1	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)
Preferred Term 2	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)

Sample Adverse Event Summary Layout 2: All treatment emergent adverse events will be provided in format 2. The system organ classes and preferred terms will be sorted by alphabetical order of system organ class and descending incidence of preferred term within each system organ class.

Phase 1:

Subject Incidence of Treatment-emergent Adverse Events by System Organ Class and Preferred Term (Worst Severity)

	Cohort A1				Cohort <B1 or A2 or not present>				Cohort <B2 or A3 or not present>			
	Any	Gr 3	Gr 4	Gr 5	Any	Gr 3	Gr 4	Gr 5	Any	Gr 3	Gr 4	Gr 5
Any <AE Descriptor> Adverse Event – n(%)	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)
System Organ Class 1	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)
Preferred Term 1	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)
Preferred Term 2	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)
System Organ Class 2	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)
…												

Phase 2:

Subject Incidence of Treatment-emergent Adverse Events by System Organ Class and Preferred Term (Worst Severity)

	Cohort 1: DLBCL				Cohort 2: PMBCL/TFL				All Phase 2			
	Any	Gr 3	Gr 4	Gr 5	Any	Gr 3	Gr 4	Gr 5	Any	Gr 3	Gr 4	Gr 5
Any <AE Descriptor> Adverse Event – n(%)	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)
System Organ Class 1	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)
Preferred Term 1	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)
Preferred Term 2	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)

System Organ Class 2 …	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)		

Sample Adverse Event Summary Layout 3: All treatment emergent adverse events will be provided in format 3 **for each phase 1 dosing cohort, for each cohort in phase 2, and for phase 2 overall.** The preferred terms will be sorted in descending order of frequency

Subject Incidence of Treatment-emergent Adverse Events by Adverse Event Onset Time (Worst Severity)

	Conditioning Chemotherapy Period (Initiation of conditioning chemotherapy up through the day prior to cell infusion)				**KTE-C19 Treatment Period (Day 1 – 30)**				**Primary Post-treatment Safety Follow-up Period (Day 31-92)**				**Secondary Post- treatment Follow –up (≥ Day 93)**			
	Any	**Gr 3**	**Gr 4**	**Gr 5**	**Any**	**Gr 3**	**Gr 4**	**Gr 5**	**Any**	**Gr 3**	**Gr 4**	**Gr 5**	**Any**	**Gr 3**	**Gr 4**	**Gr 5**
Any adverse event – n(%)	X (X)	X (X)	X (X)	X (X)	X (X)	X (X)	X (X)	X (X)	X (X)	X (X)	X (X)	X (X)	X (X)	X (X)	X (X)	X (X)
Preferred Term 1	X (X)	X (X)	X (X)	X (X)	X (X)	X (X)	X (X)	X (X)	X (X)	X (X)	X (X)	X (X)	X (X)	X (X)	X (X)	X (X)
Preferred Term 2	X (X)	X (X)	X (X)	X (X)	X (X)	X (X)	X (X)	X (X)	X (X)	X (X)	X (X)	X (X)	X (X)	X (X)	X (X)	X (X)
Preferred Term 3	X (X)	X (X)	X (X)	X (X)	X (X)	X (X)	X (X)	X (X)	X (X)	X (X)	X (X)	X (X)	X (X)	X (X)	X (X)	X (X)
. .																

12.4 Appendix 4. Derivation of Time to Event Endpoints and Last Date Known to Be Alive

Additional detail on the derivations of Duration of Response, Duration of Response to Retreatment, Progression-free Survival, and Overall Survival is provided below.

12.4.1 Duration of response (DOR): DOR is defined only for subjects who experience an objective response and is the time from the first objective response to disease progression or **death due to disease relapse**. **Non-disease related mortality will be modeled as a competing risk.** Response and progression may be defined per Investigator read – Cheson, 2007 or Central Read – Cheson, 2007. Subjects not meeting the criteria for progression or death **due to disease relapse** by the analysis data cutoff date will be censored at their last evaluable disease assessment date. **Duration of response will be derived using disease assessments obtained on study prior to initiation of new anticancer therapy (excluding ASCT). Disease assessments obtained after ASCT will be used in the derivation of duration of response. A sensitivity analysis will be conducted in which disease assessments obtained after ASCT are not included in the derivation of duration of response.**

Primary analysis of DOR:

Circumstance	**Event / Censored**	**Date of Event / Censoring**
Progression per Cheson 2007 at a scheduled assessment or in between scheduled assessments and **prior to initiation of new anticancer therapy (excluding ASCT)**	Event	Progression date
Progression per Cheson 2007 at a scheduled assessment or in between scheduled assessments and **after ASCT**	Event	Progression date
Remain in response per Cheson 2007 at a scheduled assessment or in between scheduled assessments and **after ASCT**	Censored	Last evaluable disease assessment date
Death **due to disease progression (at any time)**	Event	Death date
Non-disease related death (at any time)	**Competing risk event**	**Death date**
New anti-cancer therapy started before documented progression	Censored	Date of last evaluable disease assessment prior to initiation of new therapy
Progression or death documented after data cutoff for analysis	Censored	Date of last evaluable disease assessment prior to data cutoff for analysis
Withdrawal of consent or lost to follow-up prior to documented progression	Censored	Date of last evaluable disease assessment prior to data cutoff for analysis

Sensitivity analysis of DOR (censoring at ASCT):

Circumstance	**Event / Censored**	**Date of Event / Censoring**
Progression per Cheson 2007 at a scheduled assessment or in between scheduled assessments and **prior to initiation of new anticancer therapy (excluding ASCT)**	Event	Progression date
Progression per Cheson 2007 at a scheduled assessment or in between scheduled assessments and **after ASCT**	Censored	Last evaluable disease assessment date prior to ASCT
Remain in response per Cheson 2007 at a scheduled assessment or in between scheduled assessments and **after ASCT**	Censored	Last evaluable disease assessment date prior to ASCT
Death **due to disease progression (at any time)**	Event	Death date
Non-disease related death (at any time)	**Competing risk event**	**Death date**
New anti-cancer therapy started before documented progression	Censored	Date of last evaluable disease assessment prior to initiation of new therapy
Progression or death documented after data cutoff for analysis	Censored	Date of last evaluable disease assessment prior to data cutoff for analysis
Withdrawal of consent or lost to follow-up prior to documented progression	Censored	Date of last evaluable disease assessment prior to data cutoff for analysis

12.4.2. Duration of response to retreatment (DORR): DORR is defined only for subjects who experience an objective response to retreatment and is the time from the first objective response after retreatment to disease progression after retreatment or **death due to disease relapse**. **Non-disease related mortality will be modeled as a competing risk.** Response and progression may be defined per Investigator read – Cheson, 2007 or Central Read – Cheson, 2007. Subjects not meeting the criteria for progression after retreatment or death **due to disease relapse** by the analysis data cutoff date will be censored at their last evaluable disease assessment date after retreatment. **DORR will be derived using disease assessments obtained on study prior to initiation of new anticancer therapy (excluding ASCT). Disease assessments obtained after ASCT will be used in the derivation of DORR. A sensitivity analysis may be conducted in which disease assessments obtained after ASCT are not included in the derivation of DORR.**

Primary analysis of DORR:

Circumstance	**Event / Censored**	**Date of Event / Censoring**
Progression per Cheson 2007 at a scheduled assessment or in between scheduled assessments and **prior to initiation of new anticancer therapy (excluding ASCT)**	Event	Progression date
Progression per Cheson 2007 at a scheduled assessment or in between scheduled assessments and **after ASCT**	Event	Progression date
Remain in response per Cheson 2007 at a scheduled assessment or in between scheduled assessments and **after ASCT**	Censored	Last evaluable disease assessment date
Death **due to disease progression (at any time)**	Event	Death date
Non-disease related death (at any time)	**Competing risk event**	**Death date**
New anti-cancer therapy started before documented progression	Censored	Date of last evaluable disease assessment prior to initiation of new therapy
Progression or death documented after data cutoff for analysis	Censored	Date of last evaluable disease assessment prior to data cutoff for analysis
Withdrawal of consent or lost to follow-up prior to documented progression	Censored	Date of last evaluable disease assessment prior to data cutoff for analysis

All references to progression in the table above refer to progression after retreatment.

Sensitivity analysis of DORR (censoring at ASCT):

Circumstance	Event / Censored	Date of Event / Censoring
Progression per Cheson 2007 at a scheduled assessment or in between scheduled assessments and **prior to initiation of new anticancer therapy (excluding ASCT)**	Event	Progression date
Progression per Cheson 2007 at a scheduled assessment or in between scheduled assessments and **after ASCT**	Censored	Last evaluable disease assessment date prior to ASCT
Remain in response per Cheson 2007 at a scheduled assessment or in between scheduled assessments and **after ASCT**	Censored	Last evaluable disease assessment date prior to ASCT
Death **due to disease progression (at any time)**	Event	Death date
Non-disease related death (at any time)	**Competing risk event**	**Death date**
New anti-cancer therapy started before documented progression	Censored	Date of last evaluable disease assessment prior to initiation of new therapy
Progression or death documented after data cutoff for analysis	Censored	Date of last evaluable disease assessment prior to data cutoff for analysis
Withdrawal of consent or lost to follow-up prior to documented progression	Censored	Date of last evaluable disease assessment prior to data cutoff for analysis

All references to progression in the table above refer to progression after retreatment.

12.4.3 Progression-free Survival (PFS): PFS is defined as the time from the KTE-C19 infusion date to the date of disease progression or death from any cause. Progression may be defined per Investigator read – Cheson, 2007 or Central Read – Cheson, 2007. Subjects not meeting the criteria for progression by the analysis data cutoff date will be censored at their last evaluable disease assessment date. **PFS will be derived using disease assessments obtained on study prior to initiation of new anti-cancer therapy (excluding ASCT). Disease assessments after ASCT will be used in the derivation of PFS.**

Primary analysis of PFS:

Circumstance	**Event / Censored**	**Date of Event / Censoring**
Progression per Cheson 2007 at a scheduled assessment or in between scheduled assessments and **prior to initiation of new anticancer therapy (excluding ASCT)**	Event	Progression date
Progression per Cheson 2007 at a scheduled assessment or in between scheduled assessments **after ASCT**	Event	Progression date
Remain in response per Cheson 2007 at a scheduled assessment or in between scheduled assessments **after ASCT**	Censored	Assessment date
Death (at any time) before documented progression	Event	Death date
New anti-cancer therapy started before documented progression	Censored	Date of last evaluable disease assessment prior to initiation of new therapy
Progression or death documented after data cutoff for analysis	Censored	Date of last evaluable disease assessment prior to data cutoff for analysis
Withdrawal of consent or lost to follow-up prior to documented progression	Censored	Date of last evaluable disease assessment prior to data cutoff for analysis

12.4.4 Overall Survival (OS): OS is defined as the time from the KTE-C19 infusion to the date of death from any cause. Subjects who have not died by the analysis data cutoff date will be censored at their last contact date prior to the data cutoff date with the exception that subjects known to be alive or determined to have died after the data cutoff date for each analysis will be censored at the data cutoff date.

Circumstance	Event / Censored	Date of Event / Censoring
Death before data cutoff date for analysis	Event	Date of death
Death after data cutoff date for analysis	Censored	Data cutoff date
Known to be alive after data cutoff date for analysis	Censored	Data cutoff date
Alive up through data cutoff date and no further information available after data cutoff date	**Censored**	**Last contact date up through the data cutoff date**
Withdrawal of consent or lost to follow up prior to data cutoff date	Censored	Last date known to be alive prior to consent withdrawal or lost to follow up

12.4.5 Last date known to be alive

The last date known to be alive with be derived by obtaining the maximum complete date among the following data modules:

- Start date of AE (including targeted AE)
- Leukapheresis dates
- Conditioning chemo admin dates
- KTE-C19 infusion dates
- CT scan dates
- PET scan dates
- Clinical symptoms of lymphoma assessment dates
- Target lesion assessment
- Non-target lesion assessment
- New lesion assessment
- Disease response assessment
- Long term follow up subject status date where status = ‘alive’
- **End of treatment disposition where status is not equal to death, lost to follow up**
- End of post-treatment assessment period where status is not equal to death, lost to follow up
- End of study data where end of study reason is not equal to death, lost to follow up

Sponsor:	Kite Pharma, Inc. 2225 Colorado Avenue Santa Monica, CA 90404 United States of America
Product Name:	KTE-C19
Version Number:	Version 2.0
Release Date:	
Replaces Previous Version:	Not applicable
Date:	28 Aug 2016

Table of Contents

1. Introduction

This statistical analysis plan provides the pre-specification and details for the statistical analyses outlined within protocol KTE-C19-101 entitled "A Phase 1-2 Multi-Center Study Evaluating the Safety and Efficacy of KTE-C19 in Subjects with Refractory Aggressive Non-Hodgkin Lymphoma (NHL)", dated **12 Aug 2016.** The scope of this plan includes the interim, primary, and final analyses that are planned.

2. Objectives

The primary objective of phase 1 is to evaluate the safety of KTE-C19 regimens.

The primary objective of phase 2 is to evaluate the efficacy of KTE-C19, as measured by objective response rate in subjects with diffuse large B cell lymphoma (DLBCL), primary mediastinal B cell lymphoma (PMBCL), and transformed follicular lymphoma (TFL). Secondary objectives include assessing the safety and tolerability of KTE-C19 and additional efficacy endpoints as outlined below.

3. Study Overview

3.1 Study Design

Study KTE-C19-101 is a phase 1-2 multicenter, open-label study evaluating the safety and efficacy of KTE-C19 in subjects with refractory aggressive NHL. The trial will be separated into two distinct phases designated as phase 1 and phase 2.

For both phase 1 and phase 2, subjects will undergo

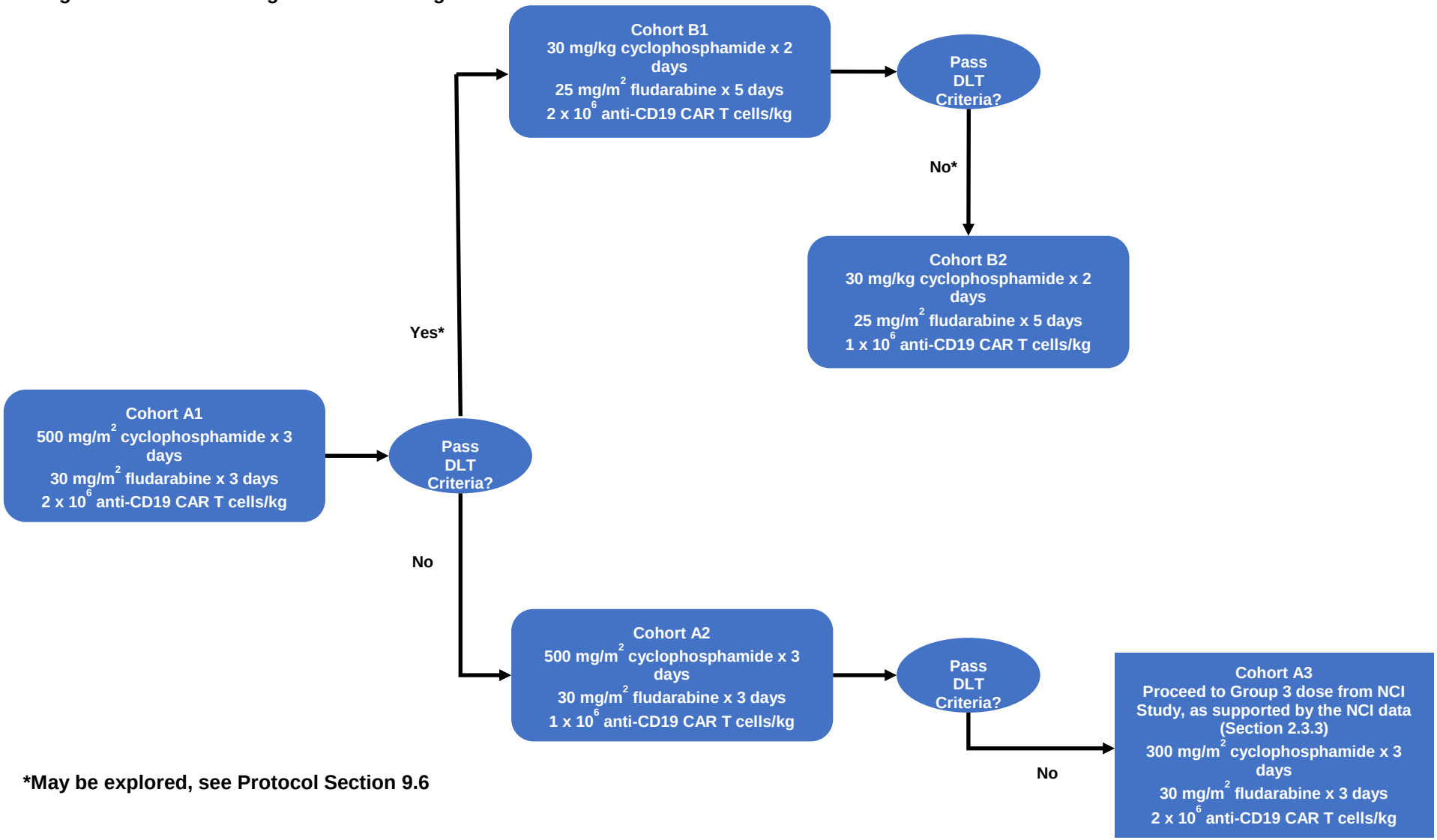
- Leukapharesis
- Conditioning chemotherapy treatment
- Investigational product treatment consisting of Chimeric Antigen Receptor (CAR) positive (+) T cells (KTE-C19)
- Post treatment assessment
- Long term follow-up

Further details on study procedures may be found in the study protocol.

During phase 1, approximately 6-24 subjects with refractory diffuse large B cell lymphoma (DLBCL), primary mediastinal B cell lymphoma (PMBCL), or transformed follicular lymphoma (TFL) will be enrolled to evaluate the safety of KTE-C19 regimens. If the initial regimen is determined to be safe, a higher dose of conditioning chemotherapy may be investigated. If the regimen is determined to not be safe, reduced doses of conditioning chemotherapy and/or KTE-C19 may be explored. A safety review team (SRT), internal to the study sponsor, will review the safety data and make

recommendations on further study conduct of phase 1 and progression to phase 2 as depicted in Figure 1 and outlined in Figure 3.

Figure 1. Phase 1 Dosing Cohorts and Regimens



***May be explored, see Protocol Section 9.6**

In phase 2, subjects will enroll into 3 separate cohorts designated as cohort 1, cohort 2, and cohort 3.

- Cohort 1 will enroll adult subjects with refractory DLBCL
- Cohort 2 will enroll adult subjects with refractory PMBCL and TFL
- Cohort 3 will enroll adult subjects with relapsed / refractory transplant ineligible DLBCL, PMBCL, or TFL

An independent data safety monitoring board (DSMB) will review safety and efficacy during the phase 2 portion of the study after 20 and 50 subjects in the mITT set in cohort 1 have had the opportunity to complete the disease assessment at 3 months post KTE-C19 infusion. The DSMB will also meet to review cohort 3 safety data when 20 subjects in cohort 3 have been treated with the target dose of KTE-C19 and have had the opportunity to be followed for 30 days.

The primary analysis of efficacy endpoints will be based on investigator review of disease assessments and evaluated per the revised International Working Group Criteria for Malignant Lymphoma (Cheson, 2007), henceforth referred to throughout this document as "Investigator read - Cheson, 2007". Secondary efficacy analyses will be based on central radiologic review of disease assessments per Cheson, 2007; these assessments will be referred to throughout this document as "Central read – Cheson, 2007". The central radiologic review will also assess disease per Cheson, 2014; analyses based on these criteria are exploratory.

3.2 Hypothesis

Cohort 1 and Cohort 2: This study is designed to differentiate between a treatment that has a true response rate of 20% or less and a treatment with a true response rate of 40% or more. The hypothesis is that the objective response rate to KTE-C19 in cohorts 1 and 2 is significantly greater than 20%.

Cohort 3: No hypothesis will be tested in cohort 3. Cohort 3 is designed to estimate the response rate in relapsed / refractory transplant ineligible DLBCL, PMBCL, or TFL.

3.3 Sample Size Considerations

The anticipated enrollment in this study is approximately 148 to 166 subjects.

Six to 24 subjects will be enrolled into phase 1 of this study.

If the study proceeds to phase 2, approximately 72 subjects will be enrolled into cohort 1 and approximately 20 subjects will be enrolled into cohort 2. Up to 50 subjects will be enrolled into Cohort 3.

As indicated in section 3.1, KTE-C19 may be dosed at doses ranging from 1 x 10^6 to 2 x 10^6 mg/kg. The target dose of KTE-C19 for each cohort is provided in Table 1.

Table 1. Planned and Target Doses of KTE-C19

Cohort	Regimen and Planned Dose of KTE-C19	Target Dose of KTE-C19
A1	500 mg/m^2 cyclophosphamide x 3 days 30 mg/m^2 fludarabine x 3 days 2 x 10^6 anti-CD19 CAR T cells/kg	• 2 x 10^6 (+/- 20%) (1.6 x 10^6 up to and including 2.4 x 10^6) anti-CD19 CAR T cells/kg • For subjects weighing > 100 kg, a maximum flat dose of 2 x 10^8 anti-CD19 CAR T cells
B1	30 mg/kg cyclophosphamide x 2 days 25 mg/m^2 fludarabine x 5 days 2 x 10^6 anti-CD19 CAR T cells/kg	• 2 x 10^6 (+/- 20%) (1.6 x 10^6 up to and including 2.4 x 10^6) anti-CD19 CAR T cells/kg • For subjects weighing > 100 kg, a maximum flat dose of 2 x 10^8 anti-CD19 CAR T cells
B2	30 mg/kg cyclophosphamide x 2 days 25 mg/m^2 fludarabine x 5 days 1 x 10^6 anti-CD19 CAR T cells/kg	• 1 x 10^6 (+/- 20%) (0.8 x 10^6 up to and including 1.2 x 10^6) anti-CD19 CAR T cells/kg • For subjects weighing > 100 kg, a maximum flat dose of 1 x 10^8 anti-CD19 CAR T cells
A2	500 mg/m^2 cyclophosphamide x 3 days 30 mg/m^2 fludarabine x 3 days 1 x 10^6 anti-CD19 CAR T cells/kg	• 1 x 10^6 (+/- 20%) (0.8 x 10^6 up to and including 1.2 x 10^6) anti-CD19 CAR T cells/kg • For subjects weighing > 100 kg, a maximum flat dose of 1 x 10^8 anti-CD19 CAR T cells
A3	300 mg/m^2 cyclophosphamide x 3 days 30 mg/m^2 fludarabine x 3 days 2 x 10^6 anti-CD19 CAR T cells/kg	• 2 x 10^6 (+/- 20%) (1.6 x 10^6 up to and including 2.4 x 10^6) anti-CD19 CAR T cells/kg • For subjects weighing > 100 kg, a maximum flat dose of 2 x 10^8 anti-CD19 CAR T cells
Phase 2 (all cohorts)	500 mg/m^2 cyclophosphamide x 3 days 30 mg/m^2 fludarabine x 3 days 2 x 10^6 anti-CD19 CAR T cells/kg	• 1 x 10^6 to 2 x 10^6 anti-CD19 CAR T cells/kg • For subjects weighing > 100 kg, a maximum flat dose of 2 x 10^8 anti-CD19 CAR T cells

Efficacy analyses will be based on a modified intent to treat (mITT) population consisting of all subjects enrolled in the phase 2 portion of the study who receive the target dose of KTE-C19.

Safety analyses will be based on all subjects dosed with KTE-C19.

DLT analyses will be based on the DLT evaluable set, defined in Section 6.6.

Inferential testing will be performed for efficacy for phase 2 cohorts 1 and 2. For cohort 3, the primary efficacy objective will be to estimate the response rate with KTE-C19 treatment in subjects with relapsed / refractory transplant ineligible DLBCL, PMBCL, or TFL.

Primary analyses of cohort 1, cohorts 1 and 2 combined, and cohort 3 are specified separately. If subject accrual and treatment is such that the primary analysis of cohort 1 occurs at the same time as the primary analysis of cohorts 1 and 2, then one clinical study report (CSR) will be written that includes both the primary analysis of cohort 1 and the primary analysis of cohorts 1 and 2 combined. Otherwise, the primary analysis CSR will be written when the first primary analysis occurs. The CSR will be amended with the results of the primary analysis of cohort 3.

3.3.1 Phase 2, Cohorts 1 and 2

This study uses a single arm design to test for an improvement in response rate in the DLBCL cohort (n=72) and in cohorts 1 and 2 combined (n=92). For the test of efficacy, this study has ≥ 90% power to distinguish between an active therapy with a 40% true response rate from a therapy with a response rate of 20% or less with a 1-sided alpha of 0.025.

The overall 1-sided alpha level of 0.025 will be divided between the inference on cohort 1 and the inference in cohorts 1 and 2 combined using the methodology described in Song, 2007 and Wang, 2007. Using this methodology, the objective response rate for cohort 1 will be tested at a 1-sided alpha level of 0.022 and the objective response rate in cohorts 1 and 2 combined will be tested at a 1-sided alpha level of 0.0075. The derivation of these alpha levels is provided in Appendix 1.

Within cohort 1, 2 interim and 1 primary analyses will be performed.

- Interim analysis 1 will be conducted after 20 subjects in the mITT set of cohort 1 have had the opportunity to be evaluated for response 3 months after the KTE-C19 infusion. This interim analysis will be for futility only. This futility analysis is based on a rho (parameter=0.35) beta spending function, with a nominal alpha level for the assessment of futility of 0.393. If the criteria for futility are not met, accrual to phase 2 will continue. Under the null hypothesis, the likelihood of stopping for futility at this analysis is 63%.
- Interim analysis 2 will be conducted after 50 subjects in the mITT set of cohort 1 have had the opportunity to be evaluated for response 3 months after the KTE-C19 infusion. This

interim analysis will assess early demonstration of efficacy. This interim analysis is based on a Pocock boundary of the Lan-DeMets family of alpha spending functions. The nominal alpha level for the assessment of efficacy for this analysis is 0.017. Under the alternative hypothesis, the likelihood of achieving the criteria for early efficacy is 84%.

- The primary analysis of cohort 1 will occur after 72 subjects in the mITT set of cohort 1 have had the opportunity to be assessed for response 6 months after the KTE-C19 infusion.

An alpha spending function will be used to allocate the alpha level between interim analysis 2 of cohort 1 and the primary analysis of cohort 1. Using the Lan-DeMets family of alpha spending functions with a Pocock boundary, the nominal 1-sided alpha used to test for efficacy at interim analysis 2 of cohort 1 is 0.017 and the nominal 1-sided alpha used to test for efficacy at the primary analysis is 0.011.

Within cohorts 1 and 2 combined, 1 primary analysis will be performed when 72 subjects in the mITT set of cohort 1 and 20 subjects in the mITT set in cohort 2 have had the opportunity to be assessed for response at 6 months after the KTE-C19 infusion. This testing will be performed at a 1-sided alpha level of 0.0075. Confidence intervals about the objective response rates within cohorts 1 and 2 will be presented with the inferential analysis of the overall study population.

As indicated above, inferential testing of cohort 1 will occur when 72 subjects in the mITT set in cohort 1 have had the opportunity to be followed for 6 months after the KTE-C19 infusion. The efficacy data from any additional subjects (beyond 72) enrolled into cohort 1 will be analyzed descriptively and **included in analyses of all secondary endpoints**. Similarly, inferential testing of cohorts 1 and 2 will occur when 72 subjects in the mITT set of cohort 1 and 20 subjects in the mITT set of cohort 2 have had the opportunity to be followed for 6 months following the KTE-C19 infusion. The efficacy data from any additional subjects (beyond 92) enrolled into cohorts 1 and 2 will be analyzed descriptively. In the event that 72 subjects in the mITT set in cohort 1 and 20 subjects in the mITT set in cohort 2 are accrued at the same time, the primary analysis of cohort 1 and the primary analysis of cohorts 1 and 2 combined will be performed at the same time.

The derivation of the alpha levels for the test of cohort 1 and cohorts 1 and 2 combined were originally obtained under the assumption of 40 subjects enrolled into cohort 2. These original derivations are retained in this protocol amendment as they result in a more conservative alpha level for the test of cohort 1.

This procedure preserves the designated 1-sided alpha level of 0.025 and has ≥ 90% power. Simulation (10000 replicates) via R version 3.1.0 and EAST version 6.3 were used to evaluate the operating characteristics of this design.

3.3.2 Phase 2, Cohort 3

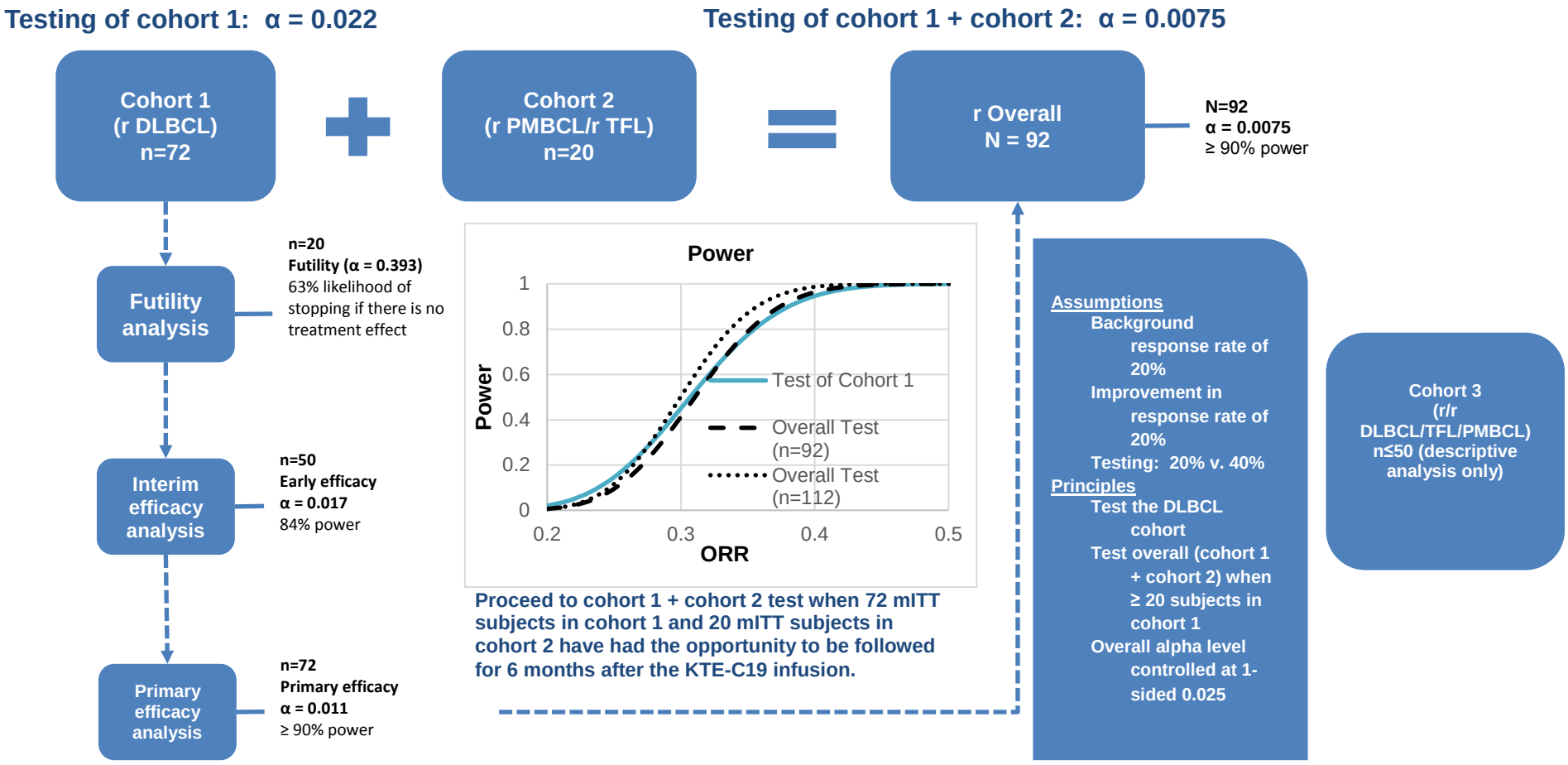
Phase 2 cohort 3 uses a single arm design to estimate the response rate in subjects with relapsed (transplant ineligible) and refractory DLBCL, PMBCL, or TFL treated with KTE-C19. The two-sided 95% confidence intervals at a range of target response rates are provided in Table 3. There are no criteria on the proportion of refractory versus relapsed subjects who will be enrolled into cohort 3 and hence a range of potential observed response rates are presented in Table 3. As indicated, with a sample size of 50 subjects the maximum width of the 95% confidence interval about response rate will be no greater than 29.

Table 2. 95% Confidence Intervals Corresponding to the Observed Objective Response Rate in Cohort 3

Observed Response Rate	**95% Confidence Interval**
40%	(27%, 55%)
50%	(36%, 65%)
60%	(45%, 73%)
70%	(56%, 82%)
80%	(67%, 90%)

A schema of the phase 2 study design is provided in Figure 2.

Figure 2. Phase 2 Study Design Schema



r - refractory
r/r = relapsed/refractory transplant ineligible

3.4 Statistical Assumptions

Phase 1 and cohorts 1 and 2 of this trial will enroll patients with chemo-refractory lymphoma, as evidenced by failure to achieve even a transient or partial response to prior biologic and combination chemotherapy or by early recurrence after ASCT.

Treatment outcomes for patients refractory to primary therapy or non-responsive to second line therapy are provided in Tables 3 and 4 below. Based on a literature review (Table 3), the response to salvage therapy for these patients ranged from 0% to 26%. Results from the international SCHOLAR-1 study (Table 4), a retrospective review of data in refractory DLBCL from 4 institutions (Crump, 2016), indicate a response rate of 26% among 597 refractory subjects. Based on these data, it is anticipated that the historical control for the objective response rate in the chemo-refractory population targeted in this study will be approximately 20%.

This study assumes that the underlying response rate (in the absence of treatment with investigational therapy) in cohorts 1 and 2 is 20% and that an improvement in the response rate to 40% provides clinically meaningful benefit.

Table 3. Literature Review of Responses in Refractory NHL (SD or PD to Last Line of Therapy)

Setting	Outcome to Subsequent Therapy
Refractory to 1st line	
Josting et al 2000 (n=64)	ORR 15%, median OS 6 mos
Phillip et al 1995 (n=28)	ORR 21%
Hitz et al 2010 (n=33)	Proceeded to ASCT 9%, 3% survived > 1 year
Ardeshna et al 2005 (n = 5)	ORR 0%
Telio et al 2012 (n = 111)	ORR 23%, median OS 10 mos
Matasar et al 2013 (n=10)	ORR 10%
Refractory to 2nd line	
Moskowitz et al 1999 (n = 55)	Median OS 5 months
Ardeshna et al 2005 (n = 28)	ORR 18%, median OS (aggressive NHL) <6 mos
Seshadri et al 2008 (n=73)	ORR 14%
Relapsed post ASCT	
Nagle et al 2013 (N=45)	Median OS 8 months

Table 4. SCHOLAR-1: Response Rate to Chemotherapy after Chemorefractory Disease (Crump, 2016)

	MDACC	MC / IA	Ly.12 (CCTG)	CORAL (LYSARC)	Integrated
Number evaluable for response	167	86	107	169	529
Response rate (%) (95% CI)	21	24	27	31	26 (22, 31)
Complete response rate (%) (95% CI)	8	7	2	15	8 (4, 15)
Partial response rate (%) (95% CI)	13	17	25	16	18 (13, 23)

MDACC – MD Anderson Cancer Center **(North America)**
MC/IA – Mayo Clinic / Iowa SPORE Database **(North America)**
LY.12 (CCTG) – Ly.12 study conducted by the Canadian Cancer Trials Group **(North America)**
CORAL (LYSARC) – CORAL study conducted by LYSARC **(EU)**

Inferential testing will not be performed in cohort 3.

4. Study Endpoints and Covariates

4.1 Endpoints

Primary (phase 1): the incidence of adverse events defined as DLTs

Primary (phase 2): the objective response rate (Investigator read - Cheson, 2007)

Secondary (phase 2**,** unless noted):

- Duration of response (Investigator read – Cheson, 2007)
- Best objective response (Investigator read - Cheson, 2007)
- Progression-free survival (Investigator read – Cheson, 2007)
- Overall survival
- Objective response rate (CR + PR) (Central read – Cheson, 2007)
- Duration of response (Central read – Cheson, 2007)
- Best objective response (Central read – Cheson, 2007)
- The incidence of adverse events, including identified and potential risks for KTE-C19
- The incidence of significant laboratory abnormalities
- The incidence and persistence of anti-KTE-C19 antibodies and anti-product impurity antibodies

- Levels and persistence of CAR T cells in blood samples
- Levels and persistence of cytokines in blood samples
- The subject incidence of replication competent retrovirus (RCR) detected in blood samples

Exploratory:

- Objective response rate (Investigator read - Cheson, 2007, Central read – Cheson, 2007) among subjects retreated with KTE-C19
- Duration of response (Investigator read – Cheson, 2007, Central read – Cheson, 2007) among subjects retreated with KTE-C19
- Change in tumor burden, as measured by baseline sum of the product of the diameters (SPD) of selected nodes or lesions to post-baseline nadir, per investigator measurements
- Change in tumor burden, as measured by baseline sum of the product of the diameters (SPD) of selected nodes or lesions to post-baseline nadir, per central read measurements
- The incidence of autologous stem cell transplant (ASCT) and allogeneic stem cell transplant (SCT) after treatment with KTE-C19
- Incidence and type of subsequent anti-cancer therapy
- Incidence of concomitant medications used to manage CRS and neurotoxicity
- Levels of lymphocyte subsets in blood samples

4.2 Covariates

The following baseline covariates may be used to examine efficacy in subgroups or covariate analyses:

- ECOG performance status at baseline
- Age at baseline (< 65, ≥ 65)
- Disease type (DLBCL, PMBCL, TFL)
- Refractory subgroup (primary refractory (refractory to first line therapy), refractory to 2nd or greater line therapy, relapse post ASCT)
- Expression of CD19 in tumor tissue prior to treatment
- **Disease stage (I-II v. III-IV)**
- **Disease extent as determined by the investigator at screening**
    - **presence of B symptoms (Y/N)**
    - **bulky disease (Y/N) (defined in Section 5.1)**
    - **extranodal disease (Y/N)**
- International prognostic index (IPI) risk category at screening
- History of bone marrow involvement
- Number of prior chemotherapy regimens (1, 2-3, ≥ 4)

- Tumor burden at baseline, as measured by the SPD of selected nodes or lesions at baseline (≤ median value, > median value)

The following baseline covariates may be used to examine safety in subgroups or covariate analyses:

- ECOG performance status at baseline
- Age at baseline (< 65, ≥ 65)
- Sex (male, female)
- Disease type (DLBCL, PMBCL, TFL)
- Refractory subgroup (primary refractory (refractory to first line therapy), refractory to 2nd or later line therapy, relapse post ASCT)
- Tumor burden at baseline, as measured by the SPD of selected nodes or lesions at baseline (≤ median value, > median value)
- IL-6 at day -5 (≤ median value, > median value)
- IL-6 at day 0 (≤ median value, > median value)
- CRP at day -5 (≤ median value, > median value)
- CRP at day 0 (≤ median value, > median value)
- Maximum value of CAR T cell expansion post-infusion (≤ median value, > median value)
- Area under the curve (AUC) of CAR T cell expansion from day 0 to day 28 (≤ median value, > median value)
- CD4/CD8 ratio of the product (≤ median value, > median value)
- % naive memory phenotype of the product (CCR7+/CD45RA+) (≤ median value, > median value)
- % central memory phenotype of the product (CCR7+/CD45RA-) (≤ median value, > median value)
- % effector memory phenotype of the product (CCR7-/CD45RA-) (≤ median value, > median value)
- % effector phenotype of the product (CCR7-/CD45RA+) (≤ median value, > median value)
- % naive + % central memory phenotype of the product (≤ median value, > median value)
- % effector memory + % effector phenotype of the product (≤ median value, > median value)
- transduction ratio of the product (≤ median value, > median value)
- total CAR T Cells of the product infused (≤ median value, > median value)
- total non-transduced T cells of the product (≤ median value, > median value)
- absolute lymphocyte count at baseline (≤ median value, > median value, missing)
- **vector copy number (VCN) of the product (≤ median value, > median value)**

The following covariates may be explored for efficacy subgroup or covariate analyses if sufficient data are present:

- Morphologic characteristics (centroblastic, immunoblastic, anaplastic, other)
- Molecular subgroup (germinal center B cell-like (GBC), activated B-cell like (ABC))
- BCL-2 alterations / overexpression (Y/N)
- BCL-6 alterations / overexpression (Y/N)
- C-MYC alterations / overexpression (Y/N)
- Double hit (C-MYC alterations or overexpression and either BCL-2 or BCL-6 alterations or overexpression) status
- Triple hit (BCL-2, BCL-6, and C-MYC alterations or overexpression) status

Covariate levels that are sparse may be collapsed for purposes of statistical modeling.

Additional associative analyses of covariates with subject outcomes will be specified in a supplemental statistical analysis plan.

5. Definitions

5.1 General

Study enrollment:

Phase 1: Study enrollment occurs when a subject has consented for the study, completes the screening criteria, receives a subject identification number, and is confirmed eligible for the study.

Phase 2: study enrollment occurs at the commencement of leukapheresis

Study day 0: Study day 0 is defined as the day the subject received the first KTE-C19 infusion. The day prior to study day 0 will be study day -1. The day of enrollment and any days after enrollment and before study day -1 will be sequential and negative integer-valued. (see leukapharesis and conditioning chemotherapy period definitions)

Leukapharesis period: the leukapharesis study period is defined as the day (negative integer valued) the subject undergoes leukapheresis calculated relative to study day 0

Conditioning chemotherapy period: the conditioning chemotherapy period begins on the day of the first chemotherapy administration until the day immediately prior to the KTE-C19 infusion. These days are numbered as sequential negative integer values, and it is anticipated that these will be as follows for the various conditioning chemotherapy regimens:

- Cohorts A1, A2, A3: Day -5 through day -1 calculated relative to study day 1, with chemotherapy administered on days -5, -4, and -3.
- Cohorts B1, B2: Day – 7 through day -1 calculated relative to study day 1, with chemotherapy administered on days -7, -6, -5, -4, -3, -2, -1.

In the event that the KTE-C19 infusion is delayed, the numbering of the conditioning chemotherapy period will remain relative to the KTE-C19 infusion.

Retreatment conditioning chemotherapy period: the retreatment conditioning chemotherapy period begins on the day of the first chemotherapy administration of retreatment until the day immediately prior to the KTE-C19 retreatment infusion. In the event that the KTE-C19 retreatment infusion is delayed, the numbering of the retreatment conditioning chemotherapy period will remain relative to the KTE-C19 retreatment infusion.

Baseline: the baseline value is defined as the last value taken prior to conditioning chemotherapy

Study therapy: study therapy is defined as conditioning chemotherapy or KTE-C19

On-study: time from enrollment to the last date of contact

Long-term follow-up period: the long-term follow-up period begins the day after the post-treatment follow-up period up through and including the 15 year survival assessment.

End of study: This will occur after all subjects have been followed for 15 years post KTE-C19 infusion, have withdrawn consent, been lost to follow-up, experienced an adverse event that precluded further follow up, or have died.

Refractory Subgroup at Baseline: Refractory subgroups are defined below. A subject may meet the criteria for multiple refractory subgroups. In this event, any subject who meets the criteria for relapse post ASCT will be categorized as such. If a subject meets more than one refractory subgroup other than relapse post ASCT, the refractory subgroup defined by the subject's last line of therapy prior to study entry will be used to categorize the subject into a refractory subgroup.

- Primary refractory: A subject is considered to be primary refractory if the subject experienced disease progression as best response to first line therapy or had stable disease after at least 4 cycles of first line therapy with duration of stable disease no longer than 6 months from the last dose of therapy.
- Refractory to 2nd or greater line therapy: A subject is considered to be refractory to 2nd or greater line therapy if the patient experienced PD as best response to the most recent therapy regimen or experienced stable disease after at least 2 cycles of therapy with duration of stable disease no longer than 6 months

- Relapse post ASCT: A subject is considered to be relapsed post-ASCT if the subject experienced relapse ≤ 12 months of ASCT.

Bulky disease: bulky disease is defined as the presence of a single lesion with largest diameter 10 cm or larger or mediastinum wider than 1/3 of the chest on a chest x-ray. The presence of bulky disease will be determined by the investigator when baseline disease extent is evaluated.

5.2 Safety

Treatment-emergent adverse event (TEAE): any adverse event with onset on or after the first dose of conditioning chemotherapy up through and including the KTE-C19 treatment period, the primary post-treatment follow-up period, the secondary post treatment follow-up period, the KTE-C19 re-treatment period (if applicable), the primary post-treatment follow up period for re-treatment (if applicable), and the secondary post-treatment follow up period for retreatment (if applicable).

KTE-C19 Treatment Period: the KTE-C19 treatment period begins the day of the first KTE-C19 infusion up through and including 30 days after the KTE-C19 infusion.

KTE-C19 Re-treatment Period: the KTE-C19 re-treatment period begins the day of the re-treatment KTE-C19 infusion up through and including 30 days after the re-treatment KTE-C19 infusion.

Primary post-treatment follow-up period: the primary post treatment follow-up period begins the day after the KTE-C19 treatment period up through and including 92 days after the KTE-C19 infusion.

Secondary post-treatment follow-up period: the secondary post treatment follow-up period begins the day after the end of the primary post-treatment safety follow-up period and continues through disease progression or the end of the 15 year survival follow up, whichever occurs first.

Primary post-treatment follow-up period for re-treatment (defined only for subjects who undergo re-treatment with KTE-C19): the primary post-treatment follow up period for re-treatment begins the day after the KTE-C19 re-treatment period up through and including 92 days after the KTE-C19 retreatment infusion.

Secondary post-treatment follow-up period for re-treatment (defined only for subjects who undergo re-treatment with KTE-C19): the secondary post-treatment follow-up period for re-treatment begins the day after the primary post-treatment follow-up period for re-treatment and continues through disease progression after re-treatment or the end of the 15 year safety follow-up, whichever occurs first. This is the follow-up period over which targeted adverse events are collected.

Deaths: All deaths that occur from the beginning of the chemotherapy conditioning period up through the end of study.

Adverse events of interest: Adverse events of interest for KTE-C19 treatment include adverse events in the categories of:

Identified risks:

- Neurological toxicity
- Cytokine-release syndrome (CRS)
- Cytopenias (including febrile neutropenia)
- B-cell aplasia

Potential risks:

- Infections
- Auto-immune disorders
- Secondary malignancies
- Tumor lysis syndrome
- Immunogenicity (anti-KTE-C19 antibodies)

Neurologic toxicity (neurotoxicity): Neurotoxicity adverse events are identified with a search strategy based on known neurologic toxicities associated with anti-CD19 immunotherapy (Topp 2015). The search strategy focuses on central nervous system toxicity, without regard to temporal relationship and concomitant conditions (eg CRS). Events are identified with a search list of MedDRA preferred terms. Additionally, a broad search strategy will be performed in which all adverse events that code into the MedDRA system organ classes of Psychiatric Disorders and Nervous System Disorders will be evaluated for potential inclusion as neurotoxicity adverse events. Neurologic toxicity will be reported separately from CRS.

CRS: CRS is identified via collection of the syndrome on a case report specifically designed to collect CRS. Specific symptoms of the CRS are collected on the adverse events log and are linked to the CRS syndrome. Adverse events of neurologic toxicity are not reported as part of the CRS syndrome as they are reported separately within the neurologic toxicity category.

Cytopenias and Febrile Neutropenia: Cytopenias (neutropenia, lymphopenia, anemia, and thrombocytopenia) are identified as:

a) adverse events with onset on or after day 21 post-anti-CD19 CAR T cell infusion with preferred terms in the MedDRA haematopoietic cytopenias standardized MedDRA Query (SMQ). The narrow version of this SMQ will be used.

b) CTCAE grade 3 or 4 laboratory toxicity for neutrophil decrease, lymphocyte decrease, hemoglobin decrease, and platelet decrease for lab assessments drawn after day 21

The incidence of cytopenias as defined by adverse events and as defined by laboratory toxicity will be summarized separately.

B-cell aplasia: Laboratory data will be used to assess the incidence and duration of B-cell aplasia, with a cut-off of B cell count < 61 B cells/µL (Kochenderfer, 2012).

Infections: Infections are identified as adverse events within the system organ class of Infections and Infestations that occur after treatment with anti-CD19 CARCAR T cells and in MedDRA high level groups (HLGT) that capture events of:

a) bacterial infection, encompassing preferred terms within the MedDRA high level group terms of
   1. bacterial infectious disorders
   2. chlamydial infectious disorders

b) viral infection, encompassing preferred terms within the MedDRA high level group term of viral infectious disorders

c) opportunistic infections, encompassing preferred terms within the MedDRA high level group terms of
   1. fungal infectious disorders
   2. mycobacterial infectious disorders

d) Other infections, encompassing preferred terms within the MedDRA high level group term of Infections – pathogen unspecified

Autoimmune disorders: Autoimmune disorders are identified via collection on a case report form in which the investigator classifies the event as an autoimmune disorder. Additionally, adverse events that are coded into the auto-immune disorders HLGT within the immune system disorders system organ class (SOC) will be reviewed to identify other potential events.

Secondary malignancy: Secondary malignancies are identified via collection on a case report form in which the investigator classifies the event as a secondary malignancy. Additionally, adverse events that are coded into the SOC of Neoplasms benign, malignant, and unspecified (including cysts and polyps) with the exception of preferred terms containing “B-cell” or “B cell” and “Lymphoma” will be reviewed to identify other potential events.

Tumor Lysis Syndrome: Tumor lysis syndrome is identified as events with MedDRA preferred terms in the Tumor Lysis Syndrome SMQ (MedDRA). The narrow version of this SMQ will be used.

5.3 Efficacy

Objective Response Rate: proportion of subjects with either a CR or PR while on study. All subjects who do not meet the criteria for objective response by the analysis data cutoff date will be considered non-responders. The derivation of this endpoint will only include response assessments obtained after the initial KTE-C19 infusion and prior to any other additional therapy (e.g. stem cell transplant or retreatment with KTE-C19). Response may be defined per Investigator read - Cheson, 2007 or Central Read – Cheson, 2007.

Duration of response (DOR): DOR is defined only for subjects who experience an objective response and is the time from the first objective response to disease progression or death due to disease relapse or drug-related toxicity. Non-disease related mortality will be modeled as a competing risk. Response and progression may be defined per Investigator read – Cheson, 2007 or Central Read – Cheson, 2007. Subjects not meeting the criteria for progression or death due to disease relapse or drug-related toxicity by the analysis data cutoff date will be censored at their last evaluable disease assessment date. For subjects who have experienced the competing risk event, DOR will be calculated as the time from the first objective response to the time of the competing risk event. DOR will be derived using disease assessments obtained on study prior to initiation of new anticancer therapy (excluding ASCT). Disease assessments obtained after ASCT will be used in the derivation of duration of response. A sensitivity analysis will be conducted in which disease assessments obtained after ASCT are not included in the derivation of DOR. Further details on the derivation of DOR are provided in Section 12.4.

Progression-free Survival (PFS): PFS is defined as the time from the KTE-C19 infusion date to the date of disease progression or death from any cause. Progression may be defined per Investigator read – Cheson, 2007 or Central Read – Cheson, 2007. Subjects not meeting the criteria for progression by the analysis data cutoff date will be censored at their last evaluable disease assessment date. PFS will be derived using disease assessments obtained on study prior to initiation of new anti-cancer therapy (excluding ASCT). Disease assessments after ASCT will be used in the derivation of PFS. Further details on the derivation of PFS are provided in Section 12.4.

Overall Survival (OS): OS is defined as the time from the KTE-C19 infusion to the date of death from any cause. Subjects who have not died by the analysis data cutoff date will be censored at their last date known to be alive prior to the data cutoff date with the exception that subjects known to be alive or determined to have died after the data cutoff date for each analysis will be censored at the data cutoff date. Further details on the derivation of overall survival and the specific data modules that will be used to derive the last date known to be alive are provided in Section 12.4.

Duration of response to retreatment (DORR): DORR is defined only for subjects who experience an objective response to retreatment and is the time from the first objective response after

retreatment to disease progression after retreatment or death due to disease relapse or drug-related toxicity. Non-disease related mortality will be modeled as a competing risk. Response and progression may be defined per Investigator read – Cheson, 2007 or Central Read – Cheson, 2007. Subjects not meeting the criteria for progression after retreatment or death due to disease relapse or drug related toxicity by the analysis data cutoff date will be censored at their last evaluable disease assessment date after retreatment. DORR will be derived using disease assessments obtained on study prior to initiation of new anticancer therapy (excluding ASCT). Disease assessments obtained after ASCT will be used in the derivation of DORR. A sensitivity analysis may be conducted in which disease assessments obtained after ASCT are not included in the derivation of DORR. Further details on the derivation of DORR are provided in Section 12.4.

6. Analysis Subsets

The following analysis sets are defined for each study phase separately.

6.1 Modified Intent-to-Treat (mITT) (defined for Phase 2)

The mITT analysis set will consist of all subjects treated with at least 1.0 x 10^6 anti-CD19 CAR T cells/kg. The mITT analysis set will be used for efficacy analyses of Phase 2.

6.2 Safety Analysis Set

The safety analysis set is defined as all subjects treated with any dose of KTE-C19.

For interim analyses, the safety set will be focused only on those subjects who have had the opportunity to be followed for one month after the KTE-C19 infusion.

6.3 Full Analysis Set (FAS)

The FAS will consist of all enrolled patients and will be used for the summary of subject disposition, sensitivity analyses of objective response rate and duration of response, and subject listings of deaths.

6.4 mITT Re-treatment Analysis Set (defined for Phase 2)

The mITT Re-treatment Analysis Set will consist of the set of all subjects who undergo re-treatment with KTE-C19 at a dose of at least 1.0 x 10^6 anti-CD19 CAR T cells/kg. This set will be used for all re-treatment efficacy analyses.

6.5. Safety Re-treatment Analysis Set

The Safety Re-treatment Analysis Set will consist of all subjects who undergo re-treatment with KTE-C19.

For interim analyses, the Safety Re-treatment set will be focused only on those subjects who have had the opportunity to be followed for one month after the re-treatment KTE-C19 infusion.

6.5 Subgroup Analysis Sets

Subgroup analyses of selected efficacy and safety endpoints may be performed for the baseline covariates defined in Section 4.2

6.6 Interim Analysis Sets

The **DLT evaluable Set(s)** (phase 1 only), defined for each dosing cohort in phase 1, will include subjects treated in the phase 1 dosing cohort who:

- Received the target and were followed for at least 30 days after the KTE-C19 infusion; or
- Received a dose of anti-CD19 CAR T cells (KTE-C19) lower than the target for that cohort and experienced a DLT during the 30 day post-infusion period.

If needed, more subjects will be enrolled to achieve 6 DLT evaluable subjects at the target dose for each cohort.

The **Futility Analysis Set** will consist of the first 20 subjects in Cohort 1 (DLBCL) who meet the criteria for the mITT analysis set and who have had the opportunity to undergo a disease assessment 3 months after the KTE-C19 infusion.

The **Interim Analysis Set** will consist of the first 50 subjects in Cohort 1 (DLBCL) who meet the criteria for the mITT analysis set and who have had the opportunity to undergo a disease assessment 3 months after the KTE-C19 infusion.

7 Interim Analysis and Early Stopping Guidelines

The SRT will review the safety data during phase 1 of the study and make a recommendation to progress the study from phase 1 to phase 2 based on the incidence of DLT and review of serious adverse events.

The DSMB will meet 3 times during the phase 2 portion of the study. The DSMB will review safety and efficacy data and will be chartered to make trial conduct recommendations based on the risk versus benefit of treatment with KTE-C19.

Additionally, as part of its oversight of the study, the DSMB will also assess criteria to pause enrollment after 10, 20, 30, and 50 subjects have been treated with KTE-C19 and have had the opportunity to be followed for 30 days. Enrollment will be paused if any of the following criteria are met:

1) subject incidence of grade 5 KTE-C19 related adverse events within 30 days is > 10%
   OR
2) subject incidence of the following grade 4 KTE-C19-related adverse events lasting more than 7 days is > 33%:
   - Neurotoxicity
   - CRS (per Lee 2014 criteria)
   - Other non-hematologic serious adverse event
   - Infection (treatment-related)

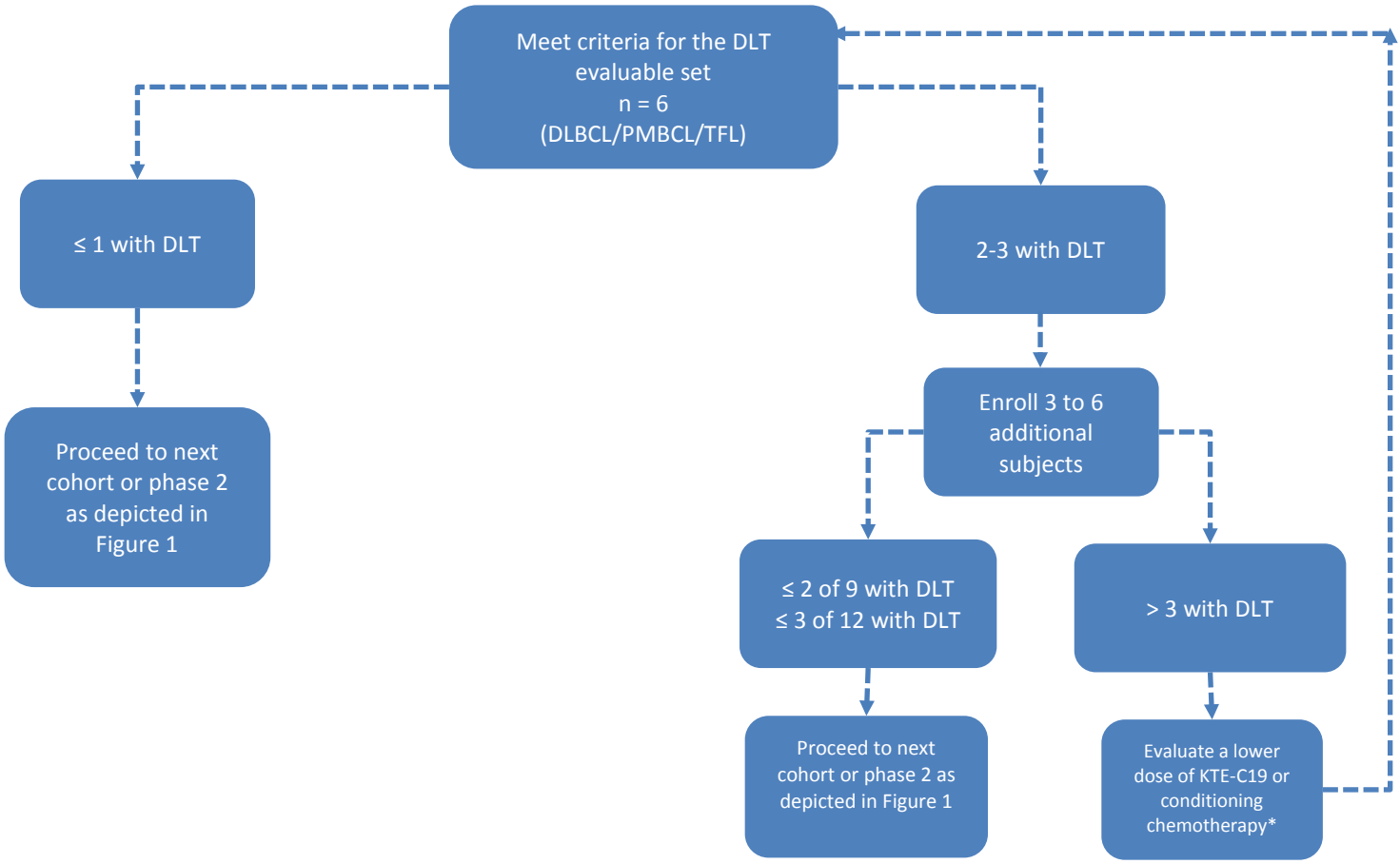
These DSMB reviews will be based on serious adverse event reports.

The DSMB may meet more often as needed.

7.1 Phase 1 – Safety Interim Analyses

The SRT will evaluate the incidence of DLTs and serious adverse events after 6 subjects, 9 subjects (if applicable), and 12 subjects (if applicable) have met the criteria for the DLT evaluable set. The SRT may recommend progression to the phase 2 portion of the trial according to the schema in Figure 3.

Figure 3. Phase 1 DLT Evaluation Scheme



*or proceed to phase 2 with the dose previously tested in the NCI study, as depicted in Figure 1.

7.2 Phase 2 – Interim Safety and Efficacy Analyses

An independent DSMB will be chartered to make recommendations on study conduct during the phase 2 portion of the study. Details may be found in the Data Safety Monitoring Board Charter. The interim efficacy analyses will be conducted on subjects in Cohort 1 who meet the criteria for the Futility and Interim analysis sets. Safety analyses will present data from both study phases and all cohorts.

The first interim efficacy analysis will be conducted after 20 subjects in the Futility Analysis Set have had the opportunity to be followed for 3 months after the KTE-C19 infusion. This interim analysis will be for safety and futility. This futility analysis is based on a rho (parameter 0.35) beta spending function. Based on this boundary, the futility criterion will be met if the p-value from this analysis is

greater than 0.393. The analysis boundary is based on a normal approximation of the binomial test; the futility analysis will be performed with an exact binomial test. Otherwise, the DSMB may recommend a change to the study conduct. Under the null hypothesis, the likelihood of stopping for futility at this analysis is 63%.

The second interim efficacy analysis will be conducted after 50 subjects in the Interim Analysis set have had the opportunity to be followed for 3 months after the KTE-C19 infusion. This interim analysis will assess safety and early demonstration of efficacy. The nominal alpha level used for the conduct of this interim analysis is 0.017 (see Section 3.3). Using this boundary, the criteria for early efficacy may be met if 17 or more subjects respond. Under the alternative hypothesis, the likelihood of meeting the criteria for early efficacy at this interim analysis is 84%.

The third interim analysis is for safety and will be conducted when 20 subjects in cohort 3 have been treated with KTE-C19 and have had the opportunity to be followed for 30 days.

After the planned primary analysis of cohort 1 and the planned primary analysis of the cohorts 1 and 2 combined, additional efficacy and safety analyses of cohorts 1 and 2 may be performed to support regulatory interaction or publications. These analyses will be descriptive. The planned primary analysis of cohort 3 will occur after all subjects treated with KTE-C19 in cohort 3 have had the opportunity to be followed for 6 months after the KTE-C19 infusion.

7.3 Access to Aggregate and Subject Level Data and Individual Subject Treatment Assignments

This study is open-label. Subjects, the study sponsor, and investigators will be aware that each subject is planned to be treated with KTE-C19. Data handling procedures designed to maintain the trial credibility and validity in this open-label single arm study are described in the Trial Integrity Document.

An independent statistician will perform the interim safety and efficacy analyses for the phase 2 portion of the study and provide these reports to the DSMB. Members of the DSMB and independent statistician will not have any direct contact with study center personnel or subjects. The DSMB will communicate recommendations to Kite Pharma in accordance with the DSMB charter.

8. Data Screening and Acceptance

8.1 General Principles

The database will be subject to the edit checks outlined in the Data Management Plan and additional manual data reviews defined by the study team. Data inconsistencies will be reviewed and resolved before the database snapshot for the primary analyses and the final database lock. For

interim analyses, snapshots may include data that has not passed all data cleaning procedures at the time the data are extracted for snapshot.

8.2 Electronic Transfer and Archival of Data

The database for this study will be managed and maintained at Theorem Clinical Research. Raw data, SDTM data, and ADaM datasets will be generated by Cytel, Inc and will be archived for all planned analyses. Any additional unplanned analyses that occur after the primary analyses and prior to the final analysis will also be archived. Key data external to the clinical study database (see below) will be included in the relevant SDTM and ADAM modules when the external data are available. For the SRT analyses, raw data may be archived and used in data review.

Data from the central pathology laboratory, the product characteristics central laboratory assessment of subject serum samples (CARCAR T cell levels in the peripheral blood, antibody assays, RCR testing), and central radiology review will be generated from contract laboratories and Kite Pharma. These data will be transferred to Theorem Clinical Research and held in a peripheral directory and not built into the clinical trial database. At the time analyses require these data, they may be merged with the SDTM and ADAM datasets.

The source and disposition of all data sources obtained from imaging vendors or laboratories is described in Appendix 2.

8.3 Handling of Missing and Incomplete Data

8.3.1 Efficacy

The method for handling missing data is described in the definition for each efficacy endpoint. Every effort will be made to obtain complete dates for deaths. In the event of a partial or missing death date and the corresponding censoring date for survival, the algorithm in Section 12.2 will be used.

8.3.2 Safety

Partial adverse event start dates will be imputed. If dates are missing or incomplete for adverse event start dates, the algorithm defined in Section 12.2 will be used. Completely missing death dates or death dates with only a year reported will not be imputed.

8.4 Detection of Bias

A listing of subjects with important protocol deviations will be generated. The deviations included in this list will include violations of eligibility criteria and use of exclusionary medication during the

study. Lack of protocol compliance will be evaluated by summarizing the subject incidence of important protocol deviations. High rates of important protocol deviations may indicate bias.

Endpoints derived from investigator assessment of radiologic scans and disease assessments may be subject to bias; the concordance between investigator and central review of radiologic scans and disease assessments will be summarized.

8.5 Outliers

Descriptive statistics will be used to identify potential outliers in any key variables analyzed. Suspected outliers will be included in all analyses unless there is sufficient scientific justification to exclude them.

8.6 Distributional Characteristics

The primary analysis of the primary endpoint is an exact binomial test used to compare the observed response rate in the cohort 1 and cohort 1 and 2 combined to a response rate of 20%. This test assumes only the independence of the individual subject responses. The validity of the assumption of a 20% historical response rate is described in Section 3.4.

An exact 95% confidence interval will be generated about the response rate. The Clopper-Pearson method will be used to generate this interval. While the Clopper-Pearson interval provides adequate coverage probability, it is commonly wider than necessary (Brown, 2002), leading to overly conservative estimates of the lower bound of objective response rate. Sensitivity analyses will be conducted in which the interval is calculated with different methods (Section 9.5.1).

8.7 Validation and Configuration Management

Programs for the development of the SDTM and ADAM datasets and the generation of the tables, figures, and listings will be developed and maintained according to Cytel, Inc Standard Operating Procedures. The software and version used to generate analyses will be indicated in the archived documentation.

9. Statistical Methods of Analysis

9.1 General Principles

The goal of the primary statistical analysis is to compare the observed response rate in cohort 1 and in cohorts 1 and 2 combined per investigator read - Cheson, 2007 to a historical control rate of 20% with an exact binomial test. Hypothesis testing will be one-sided, and all 95% confidence intervals

will be 2–sided. At the time of planned analyses, 95% confidence intervals for the response rate in each study cohort will be presented.

The timing of the interim and primary analyses will be based on subject accrual and disease assessment milestones. The primary analysis clinical study report (CSR) will be written at the primary analysis of cohorts 1 and 2 combined. If the criteria for efficacy are met at the 50-subject interim analysis, the Kite Pharma may elect to write the CSR at the time of that analysis or may write the CSR at the time of the planned primary analysis. If the primary analysis CSR is written at the time of the interim efficacy analysis, it will be amended with the results of the planned primary analysis at the time the planned primary analysis is conducted. Additionally, the CSR will be amended with the primary analysis of cohort 3 and may be amended with additional subject safety and survival follow up after the planned primary analysis.

The primary inferential efficacy analyses will include only the first 72 subjects in the cohort 1 mITT set and the first 20 subjects in the cohort 2 mITT set who have the opportunity to be followed for 6 months. If additional subjects are enrolled and treated in cohorts 1 and 2, the efficacy data from these subjects will be analyzed descriptively. Safety data from all subjects treated will be included in the primary analysis.

Analyses of the phase 1 and phase 2 portions of the study will be presented separately. Within the phase 1 summaries, each dose cohort will be presented separately. For data presented over time, assessments may be grouped into “windows” based on the actual assessment times.

9.2 Subject Accountability

The number of subjects screened, enrolled, leukapheresed, treated with conditioning chemotherapy, treated with KTE-C19, and re-treated with KTE-C19 will be summarized. The reasons for discontinuing treatment and the disease assessment and survival follow-up periods will be summarized.

Summaries of actual follow up time will be provided.

The number of subjects enrolled by country and site will be summarized.

The number of subjects in each analysis set along with reasons for exclusion will be provided.

9.3 Important Protocol Deviations

The clinical study team will define important protocol deviation categories and review all potential important protocol deviations at minimum, prior to the database snapshot for the primary efficacy analysis. Important protocol deviations will be categorized by deviation type (e.g. Entry/eligibility,

use of excluded medication). The subject incidence of important protocol deviations will be summarized overall and by deviation category.

9.4 Demographic and Baseline Characteristics

Summary statistics and frequencies for the following demographic and baseline characteristics will be tabulated:

- ECOG performance status at baseline
- Sex (male, female)
- Weight
- Age at baseline (< 65, ≥ 65)
- Race: white, Asian, other (categories may be collapsed or expanded based on accrual)
- Disease type (DLBCL, PMBCL, TFL)
- Disease subtype (DLBCL associated with chronic inflammation, EBV + DLBCL, T cell / histiocyte rich large B cell lymphoma, primary cutaneous DLBCL (leg type), DLBCL not otherwise specified, primary mediastinal (thymic) large B cell lymphoma, transformation of follicular lymphoma to DLBCL, other)
- Number of prior chemotherapy regimens
- Response to last chemotherapy regimen (PD, SD) (among subjects who are not relapsed post ASCT)
- Refractory subgroup
- Prior autologous stem cell transplant (ASCT)
- Tumor burden, as measured by the SPD of selected nodes or lesions at baseline
- Morphologic characteristics (centroblastic, immunoblastic, anaplastic, other)
- CD19 expression in tumors at baseline
- Molecular subgroup (germinal center B cell-like (GBC), activated B-cell like (ABC))
- BCL-2 alterations / overexpression (Y/N)
- BCL-6 alterations / overexpression (Y/N)
- C-MYC alterations / overexpression (Y/N)
- Double hit (C-MYC alteration/overexpression and either BCL-2 or BCL-6 alteration/overexpression) status
- Triple hit (3 of 3 recurrent chromosome translocations) status
- Disease stage (I, II, III, IV) and extent (presence of B symptoms, bulky disease, extranodal disease)
- International prognostics index (IPI) risk category
- History of bone marrow involvement

9.5 Efficacy Analyses

Efficacy analyses will be conducted on the mITT analysis set. For the primary analysis, the investigator assessment of disease status per Cheson, 2007 will be used. Sensitivity analyses will be conducted that use the central radiology review of disease assessments per Cheson, 2007. The investigator and central radiology reviewer will provide the determination of disease status (CR, PR, SD, PD, NE) at each time point. SAS programs developed by Kite Pharma and Cytel, Inc will derive the best overall response, duration of response, and progression-free survival based on these assessments.

The primary efficacy analysis will be presented in the following analysis populations:

- mITT set
- FAS set (sensitivity analysis)
- mITT set within the DLBCL cohort of the phase 2 portion of the study
- mITT set within the PMBCL / TFL cohort of the phase 2 portion of the study (descriptive analyses only)
- mITT set within cohort 3 of the phase 2 portion of the study (descriptive analyses only)
- within each cohort of the phase 1 portion of the study, including all subjects in the cohort treated at the target dose who have the opportunity to be followed for at least one disease assessment

For subjects re-treated with KTE-C19, disease assessments obtained prior to retreatment but not disease assessment obtained after retreatment will be included in the primary summaries of objective and best response, duration of response, progression-free survival, and summaries of change in tumor burden. For such subjects, disease assessments obtained after re-treatment will be included in the summaries of objective and best response to retreatment with KTE-C19 and duration of response after re-treatment with KTE-C19. The subject's overall survival time will be derived from the last date known alive regardless of re-treatment time.

In the event any subject undergoes an autologous stem cell transplant (ASCT) or any additional anti-cancer therapy while on study, the subject's best response will be derived only based on disease outcomes assessed prior to ASCT or initiation of new therapy, whichever is earlier. For subjects without documentation of progression prior to initiation of new therapy (excluding ASCT), duration of response and progression-free survival time will be censored at the last disease assessment prior to the initiation of new therapy. Disease assessments obtained after ASCT will be included in the derivation of duration of response and progression-free survival. A sensitivity analysis for duration of response and progression-free survival may be conducted in which disease assessments after ASCT are used excluded. (Appendix 12.4).

9.5.1 Objective Response and Best Response

9.5.1.1 Primary Analyses of Objective Response

The subject incidence of objective response will be calculated. An exact binomial test will be used to compare the observed response rate to the hypothesized historical control rate of 20%. The subject incidence of best response (CR, PR, SD, PD, NE, ND) will be calculated. Confidence intervals will be provided about the objective response rate, calculated with the following methods:

- Clopper-Pearson (an exact interval)
- Wilson's method (sensitivity analysis)
- Agresti-Coull method (sensitivity analysis)
- The modified Jeffrey's method (Brown, 2001) (sensitivity analysis)

The primary analysis of objective response and best response will include subjects from the phase 2 portion and will be conducted for subjects by cohort and for cohorts 1 and 2 combined. Analyses of cohort 2 alone and cohort 3 will be descriptive. The exact binomial test will not be presented for cohort 3. Sensitivity analyses of objective response will be conducted in the FAS set.

The number and percent of subjects who initially attain a partial response and subsequently attain a complete response will be summarized.

9.5.1.2 Analyses of Objective Response and Best Response per Central Read

The analyses of objective response and best response specified above will be repeated for objective response and best response per central read – Cheson, 2007.

The concordance of objective response and best objective response per investigator read – Cheson 2007 and central read – Cheson 2007 will be evaluated. A summary table of concordance, concordance rate, a kappa statistic, and a 2-sided 95% confidence interval about the kappa statistic will be provided.

Further analyses between the investigator and central reads may be described in a supplemental SAP.

9.5.1.3 Subgroup Analyses of Objective Response

Objective response rates and 95% confidence intervals about response rates will be generated for subgroups of the mITT analysis set defined by:

- ECOG performance status at baseline
- Age at baseline (< 65, ≥ 65)
- Disease type (DLBCL, PMBCL, TFL)
- Refractory subgroup
- Disease stage (I-II, III-IV)
- IPI risk category
- Number of prior chemotherapy regimens (1, 2-3, ≥ 4)
- History of bone marrow involvement
- Tumor burden, as measured by the SPD of selected nodes or lesions at baseline (≤ median, > median)
- **Expression of CD19 in tumor tissue prior to treatment**
- **Disease extent as determined by the investigator at screening**
    - **presence of B symptoms (Y/N)**
    - **bulky disease (Y/N) (defined in Section 5.1)**
    - **extranodal disease (Y/N)**

Objective response rates and 95% confidence intervals about response rates may be generated for subgroups of the mITT analysis set defined by the following covariates if sufficient data are available.

- Morphologic characteristics
- BCL-2 alterations / overexpression
- BCL-6 alterations / overexpression
- C-MYC alterations / overexpression
- Double hit status per investigator assessment
- Triple hit status per investigator assessment

A forest plot of the proportion of responders for each of these groups will be generated.

9.5.1.4 Analyses of Objective Response – Phase 1

Analyses of objective response in phase 1 may occur at any time during phase 1. The purpose of these analyses may include publications, preliminary evaluation of benefit-risk, and to inform decisions on dose.

At minimum, objective response rates and 95% confidence intervals will be generated for each dose cohort in phase 1.

9.5.2 Duration of Response

The competing-risk analysis method (Pepe, 1993, Fine and Gray, 1999) will be used to estimate the cumulative incidence of relapse/disease-related death in the presence of non-disease related mortality. The cumulative incidence (CIF) for relapse/disease-related death in the presence of non-disease related mortality will be estimated and 1- CIF will be used to estimate the relapse-free rate at 3-month time intervals. A stacked plot of the CIF for relapse / disease-related death in the presence of non-disease-related mortality and the CIF for non-disease-related mortality over time will be presented. The number of subjects censored, the reasons for censoring, and the number of subject experiencing the competing risk will be summarized. Additionally, multi-state time to event models may be used to estimate the hazard of death after relapse (illness-death model) and the hazard of relapse in the presence of non-disease related mortality (competing-risk model) (Putter, 2007). The number of subjects censored and the reasons for censoring will be summarized. Analyses will be generated for duration of response per investigator read – Cheson, 2007 and duration of response per central read – Cheson, 2007. The reverse Kaplan-Meier approach (Schemper, 1996) will be used to estimate the follow up time for duration of response.

In the event that no competing risk events have occurred at the time of any analysis, the Kaplan-Meier approach will be used to estimate duration of response.

Duration of response will also be presented stratified by subjects who undergo ASCT after treatment with KTE-C19 v. subjects who do not undergo ASCT after treatment with KTE-C19.

Sensitivity analyses of objective response will be conducted in the FAS sets.

A sensitivity analysis of duration of response will be conducted in which the duration of response for subjects undergoing ASCT is censored at the last evaluable disease assessment prior to ASCT.

9.5.3 Progression-free Survival

Kaplan-Meier plots, estimates and 2-sided 95% confidence intervals will be generated for progression-free survival. Estimates of the proportion of subjects alive and progression-free at 3 month intervals will be provided. The number of subjects censored and the reasons for censoring will be summarized. Analyses will be generated for progression-free survival per investigator read – Cheson, 2007 and progression-free survival per central read – Cheson, 2007.

Additionally, multi-state time to event models may be used to estimate the hazard of death after progression (illness-death model) (Putter, 2007).

9.5.4 Overall Survival

The analysis of overall survival will use the same methods as the analysis of progression-free survival (with the exception of the concordance analysis between the investigator and radiology vendor). The reverse Kaplan-Meier approach (Schemper, 1996) will be used to estimate the follow up time for overall survival.

A graphical summary of the time to response, duration of response, retreatment, progression, and death times from the time of KTE-C19 infusion depicted on a horizontal time axis for each patient ("swim lane plot") will be provided.

9.5.5 Tumor Burden

The change in tumor burden, as measured by the sum of the products of the diameters of the selected lesions, from baseline to post-baseline nadir will be summarized in absolute numbers (mm^2) and percentage. A graphical summary of this change will be presented in a vertical bar chart with each subject's change from baseline to nadir displayed as a vertical bar, with color coding that indicates best response attained ("waterfall" plot). Summary statistics will be provided for this change. Additionally, plots over time of the percent change in tumor burden for each subject (superimposed on one graph) will be presented. Analyses will be generated for change in tumor burden per investigator read and per central read.

9.5.6 Objective Response and Best Response Among Subjects Re-treated with KTE-C19

The subject incidence of subjects re-treated with KTE-C19 will be tabulated. The subject incidence of objective response and best response (CR, PR, SD, PD, NE, ND) to the retreatment among subjects re-treated with KTE-C19 will be calculated. Confidence intervals will be provided about the objective response rate to the retreatment. Analyses may be conducted per investigator read – Cheson 2007 and central read – Cheson 2007.

9.5.7 Duration of Response Among Subjects Re-treated with KTE-C19

The analysis of duration of response to retreatment among subjects re-treated with KTE-C19 will use the same methods as the analysis of duration of response.

9.5.8 Incidence of ASCT

The subject incidence of ASCT post-treatment with KTE-C19 will be tabulated.

9.6 Safety Analyses

Safety analyses will be conducted on the safety analysis set. The primary analysis of safety data will summarize all treatment-emergent adverse events and laboratory values. Additional summary tables will present all treatment emergent adverse events, as well as adverse events with onset time categorized by study treatment period (conditioning chemotherapy treatment period, KTE-C19 treatment period, primary post-treatment follow up period, and secondary post-treatment follow up period). For subjects who undergo retreatment with KTE-C19, adverse events occurring in the KTE-C19 re-treatment period may be summarized in an additional separate summary that presents only the AEs occurring during the KTE-C19 retreatment period. Sample table layouts are provided in Appendix 3.

Adverse events will be coded with the Medical Dictionary for Regulatory Activities (MedDRA) at the time of each analysis. The version of the MedDRA may vary over time as the current version in use is updated. The severity of adverse events will be graded using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. Cytokine release syndrome (CRS) will be graded using a revised CRS grading scale developed by Lee et al (Lee, 2014) and per CTCAE 4.03. The incidence and severity of CRS will be reported as a syndrome with severity per Lee et al. Individual symptoms associated with CRS will be graded per CTCAE version 4.03.

Deaths due to disease progression will be denoted as such on case report forms.

Subjects enrolled but not dosed with KTE-C19 will be followed for adverse events for 30 days after the last study procedure. Adverse events reported in these patients will be archived in the study database and available in SDTM and ADAM datasets, but will not be tabulated in adverse event summaries.

Safety summaries will be presented separately for each phase 1 dosing cohort and for phase 2 by cohort and overall.

9.6.1 Adverse Events

The subject incidence of the following treatment-emergent adverse events will be tabulated for the:

- Summary of adverse events (any, worst severity, serious, related)
- All adverse events
- All serious adverse events
- All leukapheresis-related adverse events
- All conditioning-chemotherapy-related adverse events
- All KTE-C19-related adverse events

- All conditioning chemotherapy-related serious adverse events
- All KTE-C19-related serious adverse events
- All grade 3 or higher adverse events
- All grade 3 or higher conditioning chemotherapy-related adverse events
- All grade 3 or higher KTE-C19-related adverse events
- Fatal adverse events
- Adverse events of interest, including identified risks (CRS, neurotoxicity, B-cell aplasia, and cytopenias (including febrile neutropenia) and potential risks (infections, auto-immune disorders, secondary malignancies, tumor lysis syndrome, and immunogenicity)

Summary statistics for the onset time (Kaplan-Meier estimates) and duration of adverse events of interest will be provided.

The subject incidence of deaths by treatment period will be provided.

A subject listing of deaths and serious adverse events (including narratives) will be provided overall and by treatment period.

A summary of demographics and baseline characteristics among subjects who experience CRS and who do not experience CRS will be provided.

Subgroup analyses of adverse events may be generated for the covariates listed in Section 4.2.

9.6.2 Procedures and Concomitant Medications

The incidences of procedure and concomitant medications used to manage adverse events will be tabulated **(see Section 9.6.7).**

9.6.3. Laboratory Test Results

Laboratory results will be graded according to NCI Common Toxicity Criteria (CTCAE version 4.0**3**). Laboratory data collected at baseline and through the KTE-C19 Treatment Period will be summarized. Shifts from baseline to minimum post-baseline and / or maximum post-baseline will be presented for select analytes. The incidence of worst grade CTCAE shift for all analytes will be provided.

9.6.4 Anti-KTE-C19 antibodies

The subject incidence of any anti-KTE-C19 antibodies and anti-product impurity antibodies will be tabulated. For subjects testing positive for antibodies, the persistence of the antibody over time will be summarized.

9.6.5 Replication Competent Retrovirus (RCR)

The subject incidence of replication competent retrovirus (RCR) detected in blood samples will be tabulated overall and by assessment time. The persistence of RCR over time will be summarized.

9.6.6 Exposure to Study Treatment and Product Characteristics

Summary statistics and subject listings will be provided for the following:

- Total BSA-adjusted dose of cyclophosphamide
- Total mg of cyclophosphamide
- Total BSA-adjusted dose of fludarabine
- Total mg of fludarabine
- Weight-adjusted dose of KTE-C19
- Total CAR T cells of the KTE-C19 infusion
- Total T cells of the KTE-C19 infusion
- Transduction ratio
- Percentages of CD4 and CD8 T cells
- Percentages of T cell memory phenotypes
- IFN-gamma production in co-cultures of KTE-C19 product and $CD19^{+}$ target cells
- **Vector copy number of KTE-C19 product**

Separate summaries will be presented for the 2^{nd} administration of conditioning chemotherapy for subjects in the Re-treatment Analysis Set.

9.6.7 Exposure to Concomitant Medications and Procedures

The subject incidence of concomitant medications will be provided and summarized by medication category (general, gamma globulin, immunosuppressive, anti-infective, vaccinations, IV normal saline bolus, and vasopressor, tocilizumab, and steroids) and WHO Drug coded term. The subject incidence of procedures will be tabulated.

9.6.8 Mini Mental Status Exam (MMSE)

Summary statistics for the MMSE score and change from baseline in the MMSE score over time will be provided for all subjects in the safety analysis set and may be summarized within groups defined by the occurrence of grade 3 or higher neurotoxicity.

9.7 Subsequent Anti-cancer Therapy

The incidence and type (by WHO Drug coded term and categories) of subsequent anti-cancer therapy and stem cell transplant (autologous, allogeneic) will be summarized.

9.8 Schedule of Study Treatment

Summary statistics will be provided for the following durations:

- Days from leukapheresis to commencement of conditioning chemotherapy
- Days from leukapheresis to administration of KTE-C19
- Days from conditioning chemotherapy to administration of KTE-C19
- Duration of hospitalization for the KTE-C19 infusion

9.9 CARCAR T cells Measured in Peripheral Blood

Summary statistics for the level of CARCAR T cells in serum post KTE-C19 infusion will be provided for CARCAR T cells measured at day 7, week 2, week 4, month 3, month 6, month 12, and month 24. The maximum CAR T cell level attained, the time at which the maximum level was attained, and the time at which there were no detectable CARCAR T cells in the serum will be summarized.

9.10 B-cell Aplasia

The subject incidence of B-cell aplasia, and the subject incidence of recovery after B-cell aplasia will be provided for each subject based on B cells measured by flow cytometry prior to conditioning chemotherapy, on the day of the KTE-C19 infusion, week 4, month 3, month 6, month 9, month 12, month 15, month 18, and month 24The onset and duration of B-cell aplasia will be summarized; the duration of these events for subjects with B-cell aplasia ongoing at the last measurement will be censored at that time. The use of IVIG treatment in the presence of B cell aplasia may be summarized.

10. Changes from Protocol-Specified Analyses

The following changes have been made between this SAP and protocol version 5.0 (amendment #2), dated 12 Aug 2016.

- Additional exploratory endpoints have been added as described below:
  - Progression-free survival per central read – Cheson 2007
  - Changes in tumor burden per investigator assessment
  - Changes in tumor burden per central read
  - Incidence of autologous stem cell transplant after treatment with KTE-C19

- Schedule of study treatment
- Incidence and type of subsequent anti-cancer therapy

The rationale for the addition of these endpoints is that these endpoints are useful to more thoroughly characterize the efficacy, safety, and logistical management of treatment with KTE-C19.

11. References

Ardeshna KM, Kakouros N, Qian W, et al. Conventional second-line salvage chemotherapy regimens are not warranted in patients with malignant lymphomas who have progressive disease after first-line salvage therapy regimens. *Br J Haematol.* 2005 Aug;130(3):363-72.

Brown SD, Cai TT, and DasGupta A. Interval Estimation for a Binomial Proportion. *Statistical Science.* 2001;16:101-133.

Brown LD, Cai TT, DasGupta A. Confidence Intervals for a Binomial Proportion and Asymptotic Expansions. *The Annals of Statistics.* 2002; 30:160-201.

Cheson BD, Pfistner B, Juweid ME, Gascoyne RD, Specht L, Horning SJ, et al. Revised response criteria for malignant lymphoma. *J Clin Oncol.* 2007;25(5):579

Cheson BD, Fisher RI, Barrington SF, Cavalli F, Schwartz LH, Zucca E, and Lister TA. Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification, *J Clin Oncol.* 2014.

Crump M, et al. Randomized Comparison of Gemcitabine, Dexamethasone, and Cisplatin Versus Dexamethasone, Cytarabine, and Cisplatin Chemotherapy Before Autologous Stem-Cell Transplantation for Relapsed and Refractory Aggressive Lymphomas: NCIC-CTG LY.12, *J Clin Oncol*., 2014; 32:3490-3496.

Fine J, Gray RA. Proportional hazards model for the subdistribution of a competing risk. *J American Statistical Assoc* 1999;94(446):496-509.

Hitz F, Connors JM, Gascoyne RD, Outcome of Patients with Chemotherapy Refractory and Early Progressive Diffuse Large B Cell Lymphoma After R-CHOP Treatment; *Blood* (ASH Annual Meeting Abstracts, Poster Session) 2010 116: Abstract 1751

Josting A, et al. Prognostic factors and treatment outcome in primary progressive Hodgkins Lymphoma: a report from the German Hodgkin study group; *Blood* 2000 August 15; 96: 1280-1286.

Klein JP, Moeschberger ML, Survival Analysis: Techniques for Censored and Truncated Data. Springer, 2005.

Kochenderfer J, Dudley M, Feldman S, et al. B-cell depletion and remissions of malignancy along with cytokine-associated toxicity in a clinical trial of anti-CD19 chimeric-antigen-receptor–transduced T cells. *Blood* 2012;119:2709-2720.Lan-Demets/Pocock: KK Gordon Lan and David L. DeMets, Discrete sequential boundaries for clinical trials, I 983; 70:3:659-663.

Matasar MJ, Czuczman MS, Rodriguez MA, et al. Ofatumumab in combination with ICE or DHAP chemotherapy in relapsed or refractory intermediate grade B-cell lymphoma. *Blood.* 2013; 122(4):499-506

Nagle SJ, Woo K, Schuster SJ, Nasta SD, Stadtmauer E, Mick R and Svoboda J. Outcomes of patients with relapsed/refractory diffuse large B-cell lymphoma with progression of lymphoma after autologous stem cell transplantation in the rituximab era. *J Hematol*. 2013; 88:890-894.

Pepe, M. Inference for events with dependent risks in multiple endpoint studies. J American Statistical Assoc 1991;86:770-778.Philip T, Guglielmi C, Hagenbeek A, et al. Autologous bone marrow transplantation as compared with salvage chemotherapy in relapses of chemotherapy-sensitive non-Hodgkin's lymphoma. *N Engl J Med.* 1995; 333: 1540-5.

Putter H, Tutorial in biostatistics: Competing risks and multi-state models. *Statistics in Medicine,* 2007; 26: 2389-2430.

Schemper M, Smith TL A note on quantifying follow-up in studies of failure time. *Control Clin Trials* 17: 343-346, 1996.

Seshadri T, Kuruvilla J, Crump M, Keating A. Salvage therapy for relapsed/refractory diffuse large B cell lymphoma. *Biol Blood Marrow Transplant.* 2008 Mar;14(3):259-67.

Song Y, Chi GYH. A method for testing a prespecified subgroup in clinical trials, *Statistics in Medicine*, 2007; 26:3535-3549

Telio D, Fernandes K, Ma C, et al. Salvage chemotherapy and autologous stem cell transplant in primary refractory diff use large B-cell lymphoma: outcomes and prognostic factors. *Leukemia & Lymphoma*. 2012; 53(5): 836-841.

Wang: Sue-Jane Wang, Approaches to evaluation of treatment effect in randomized clinical trials with genomic subset, *Pharmaceutical Statistics*, 2007; 6:227-244

12 Appendices

12.1 Appendix 1: Derivation of split alpha levels

The calculation of the split alpha levels is based on the methods in Song and Chi (2007) and Wang (2007) as follows:

- The overall alpha level is 1-sided α=0.025.
- Denote the alpha level for the test of the overall study population as α_1, with α_1=0.0075.
- The alpha level for the test of cohort 1 is denoted by α_2 and is obtained by solving the following equation for α_2:

$$\int_{-\infty}^{z_{\alpha_1}} \Phi\left(\frac{z_{\alpha_2} - \sqrt{p}\, z_1}{\sqrt{1-p}}\right) \phi(z_1) dz_1 = 1 - \alpha$$

Where $\phi(\cdot)$ is the normal density function, z_β is the normal upper 100β percentile, and p is the proportion of subjects in cohort 1 relative to the overall study population. Given that accrual to cohort 2 may range between 20 and 40 subjects, the value of α_2 obtained from the equation above when accrual to cohort 2 is 40 was used to prospectively define the split alpha levels. This value results in lower alpha levels and hence ensures control of the type I error.

12.2 Appendix 2: Source and Disposition of Non-Clinical Database Data

Sample Type	Analysis / Data Element	Testing Lab / Source	Responsible to transfer to TCR	Include in Clinical Data Submitted to FDA	Analysis Plan
Product cells	Total T cells	Batch record	Kite/TCR	Yes	Primary SAP
Product cells	Transduction ratio	Batch record	Kite/TCR	Yes	Primary SAP
Product cells	Total CARCAR T cells	Batch record	Kite/TCR	Yes	Primary SAP
Product cells	Total T Cells	Batch record	Kite/TCR	Yes	Primary SAP
Product cells	Days of manufacture	PCT / Batch record	Kite/TCR	Yes	Primary SAP
Product cells	CD4/CD8 Ratio, Memory phenotypes	Kite	Kite	No	Primary SAP and supplemental translational research SAP
Product cells	Cytokines (co culture)	Kite	Kite	No	Supplemental translational research SAP
Biospecimen (post KTE-C19 infusion samples)	Cell differentiation and phenotype	Kite	Kite	No	Supplemental translational research SAP
Biospecimen	Cytokines	Kite	Kite	No	Supplemental translational research SAP
Biospecimen	CAR PCR	URMC	URMC	Yes	Primary SAP and Supplemental translational research SAP
Biospecimen	Antibody	Alta Intertek	Alta	Yes	Primary SAP
Biospecimen	RCR	Remidion	Remidion	Yes	Primary SAP
Tissue blocks	Paired biopsy	Acteris	Acteris	No	Supplemental SAP
Tissue blocks	Pathology	NeoGenomics	NeoGenomics	Yes	Primary SAP
Independent Radiology Review	Cheson 2007	Bioclinica	Bioclinica	Yes	Primary SAP
Independent Radiology Review	Cheson 2014	Bioclinica	Bioclinica	Yes	Supplemental Concordance SAP

All data will be archived at Cytel, Inc. Data indicated as 'Yes' for inclusion in the clinical data submitted to FDA will be merged with the clinical data. Data indicated as 'No' for inclusion in the clinical data submitted to FDA will be archived at Cytel but may not merged with the clinical data.

12.2 Appendix 2: Conventions for Clinical Data That Require Imputation for Partial or Missing Dates

The following data will be imputed using the following algorithm:

- Adverse event start dates
- Deaths (please see exceptions below)
- Concomitant medication start dates
- Subsequent anti-cancer therapy start dates

Table 2. Imputation Rules for Partial or Missing Start Dates

Start Date		Stop Date: Complete: *yyyymmdd*		Stop Date: Partial: *yyyymm*		Stop Date: Partial: *yyyy*		Stop Date: Missing
		< day 1	≥ day 1	< day 1 *yyyymm*	≥ day 1 *yyyymm*	< day 1 *yyyy*	≥ day 1 *yyyy*	
Partial *yyyymm*	= day 1 *yyyymm*	2	1	2	1	n/a	1	1
	≠ day 1 *yyyymm*		2		2	2	2	2
Partial *yyyy*	=1st dose *yyyy*	3	1	3	1	n/a	1	1
	≠ 1st dose *yyyy*		3		3	3	3	3
Missing		4	1	4	1	4	1	1

1 = impute the date of day 1
2 = impute the first of the month
3 = impute January 1 of the year
4 = impute January 1 of the stop year
Note: if the start date imputation leads to a start date that is after the stop date, then do not impute the start date.
Imputation rules for partial or missing death dates:

1. If death year and month are available but day is missing:
    - If mmyyyy for the last contact date = mmyyyy for death date, set death date to the day after the last date known to be alive.
    - If mmyyyy for the last date known to be alive < mmyyyy for death date, set death date to the first day of the death month.
    - If mmyyyy for last date known to be alive > mmyyyy for death date, data error and do not impute.
2. If both month and day are missing for death date or a death date is completely missing, do not impute and censor the subject survival time at the last date known to be alive.

12.3 Appendix 3: Sample Adverse Event Table Layouts

All treatment emergent adverse events will be summarized in the AE Summary Table format below. Tables will be generated for Phase 1, Phase 2 Cohort 1, Phase 2 Cohort 2, Phase 2 Cohort 1 and 2 combined, and Phase 2 Cohort 3.

AE Summary Table Format

	(N =)
Any TEAE	X (XX)
Worst Grade 1	
Worst Grade 2	
Worst Grade 3	
Worst Grade 4	
Worst Grade 5	
Worst Grade ≥ 3	
Any Serious TEAE	
<Worst Grades as above>	
Any Conditioning Chemotherapy Related TEAE	
<Worst Grades as above>	
Any Serious Conditioning Chemotherapy Related TEAE	
<Worst Grades as above>	

Adverse Event Summary Layout 1: All AE summaries and AE subgroup analyses will be provided in format 1. The preferred terms will be sorted by descending order of frequency of the All, Any column. Tables will be generated for Phase 1, Phase 2 Cohort 1, Phase 2 Cohort 2, Phase 2 Cohort 1 and 2 combined, and Phase 2 Cohort 3.

Subject Incidence of <AE Descriptor> Adverse Events in Descending Order of Preferred Term by Worst Severity

(N =)

MedDRA Preferred Term n (%)	Any	Worst Grade 1	Worst Grade 2	Worst Grade 3	Worst Grade 4	Worst Grade 5
Any						
Preferred Term 1						
Preferred Term 2						

Adverse Event Summary Layout 2: All AE summaries and AE subgroup analyses will be provided in format 2. The preferred terms will be sorted by descending order of frequency of the All, Any column. Tables will be generated for Phase 1, Phase 2 Cohort 1, Phase 2 Cohort 2, Phase 2 Cohort 1 and 2 combined, and Phase 2 Cohort 3.

Subject Incidence of Grade 3 or Higher <AE Descriptor> Adverse Events in Descending Order of Preferred Term by Worst Severity

(N =)

MedDRA Preferred Term n (%)	Any	Worst Grade 3	Worst Grade 4	Worst Grade 5
Any				
Preferred Term 1				
Preferred Term 2				

Adverse Event Summary Layout 3: All treatment emergent adverse events will be presented in the format below. Tables will be generated for Phase 1, Phase 2 Cohort 1, Phase 2 Cohort 2, Phase 2 Cohort 1 and 2 combined, and Phase 2 Cohort 3.

Subject Incidence of <AE Descriptor> Adverse events in Descending Order of Preferred Term by Worst Severity

	Any	**Gr 3**	**Gr 4**	**Gr 5**
Any <AE Descriptor> Adverse Event – n(%)	XX (X)	XX (X)	XX (X)	XX (X)
System Organ Class 1	XX (X)	XX (X)	XX (X)	XX (X)
Preferred Term 1	XX (X)	XX (X)	XX (X)	XX (X)
Preferred Term 2	XX (X)	XX (X)	XX (X)	XX (X)
System Organ Class 2				
…				

Adverse Event Summary Layout 4: Fatal adverse events will be summarized in the format below. Tables will be generated for Phase 1, Phase 2 Cohort 1, Phase 2 Cohort 2, Phase 2 Cohort 1 and 2 combined, and Phase 2 Cohort 3.

Subject Incidence of Fatal Adverse Events

(N =)

MedDRA Preferred Term n (%)	
Any	
Preferred Term 1	
Preferred Term 2	

Sample Adverse Event Summary Layout 5: All treatment emergent adverse events will be provided in format 5 The preferred terms will be sorted in descending order of frequency **of the KTE-C19 Treatment Period Day 1-30 Any Column.** Tables will be generated for Phase 1, Phase 2 Cohort 1, Phase 2 Cohort 2, Phase 2 Cohort 1 and 2 combined, and Phase 2 Cohort 3.

Subject Incidence of Treatment-emergent Adverse Events by Adverse Event Onset Time (Worst Severity)

	Conditioning Chemotherapy Period (Initiation of conditioning chemotherapy up through the day prior to cell infusion)				KTE-C19 Treatment Period (Day 1 – 30)				Primary Post-treatment Safety Follow-up Period (Day 31-92)				Secondary Post- treatment Follow –up (≥ Day 93)			
	Any	**Gr 3**	**Gr 4**	**Gr 5**	**Any**	**Gr 3**	**Gr 4**	**Gr 5**	**Any**	**Gr 3**	**Gr 4**	**Gr 5**	**Any**	**Gr 3**	**Gr 4**	**Gr 5**
Any adverse event – n(%)	X (X)	X (X)	X (X)	X (X)	X (X)	X (X)	X (X)	X (X)	X (X)	X (X)	X (X)	X (X)	X (X)	X (X)	X (X)	X (X)
Preferred Term 1	X (X)	X (X)	X (X)	X (X)	X (X)	X (X)	X (X)	X (X)	X (X)	X (X)	X (X)	X (X)	X (X)	X (X)	X (X)	X (X)
Preferred Term 2	X (X)	X (X)	X (X)	X (X)	X (X)	X (X)	X (X)	X (X)	X (X)	X (X)	X (X)	X (X)	X (X)	X (X)	X (X)	X (X)
Preferred Term 3	X (X)	X (X)	X (X)	X (X)	X (X)	X (X)	X (X)	X (X)	X (X)	X (X)	X (X)	X (X)	X (X)	X (X)	X (X)	X (X)
.																
.																

12.4 Appendix 4. Derivation of Time to Event Endpoints and Last Date Known to Be Alive

Additional detail on the derivations of Duration of Response, Duration of Response to Retreatment, Progression-free Survival, and Overall Survival is provided below.

12.4.1 Duration of response (DOR): DOR is defined only for subjects who experience an objective response and is the time from the first objective response to disease progression or death due to disease relapse or drug-related toxicity. Non-disease related mortality will be modeled as a competing risk. Response and progression may be defined per Investigator read – Cheson, 2007 or Central Read – Cheson, 2007. Subjects not meeting the criteria for progression or death due to disease relapse by the analysis data cutoff date will be censored at their last evaluable disease assessment date. Duration of response will be derived using disease assessments obtained on study prior to initiation of new anticancer therapy (excluding ASCT). Disease assessments obtained after ASCT will be used in the derivation of duration of response. A sensitivity analysis will be conducted in which disease assessments obtained after ASCT are not included in the derivation of duration of response.

Primary analysis of DOR:

Circumstance	Event / Censored	Date of Event / Censoring
Progression per Cheson 2007 at a scheduled assessment or in between scheduled assessments and prior to initiation of new anticancer therapy (excluding ASCT)	Event	Progression date
Progression per Cheson 2007 at a scheduled assessment or in between scheduled assessments and after ASCT	Event	Progression date
Remain in response per Cheson 2007 at a scheduled assessment or in between scheduled assessments and after ASCT	Censored	Last evaluable disease assessment date
Death due to disease progression (at any time)	Event	Death date
Death due to drug-related toxicity	Event	Death date
Non-disease related death (at any time)	Competing risk event	Death date
New anti-cancer therapy started before documented progression	Censored	Date of last evaluable disease assessment prior to initiation of new therapy
Progression or death documented after data cutoff for analysis	Censored	Date of last evaluable disease assessment prior to data cutoff for analysis
Withdrawal of consent or lost to follow-up prior to documented progression	Censored	Date of last evaluable disease assessment prior to data cutoff for analysis

Sensitivity analysis of DOR (censoring at ASCT):

Circumstance	Event / Censored	Date of Event / Censoring
Progression per Cheson 2007 at a scheduled assessment or in between scheduled assessments and prior to initiation of new anticancer therapy (excluding ASCT)	Event	Progression date
Progression per Cheson 2007 at a scheduled assessment or in between scheduled assessments and after ASCT	Censored	Last evaluable disease assessment date prior to ASCT
Remain in response per Cheson 2007 at a scheduled assessment or in between scheduled assessments and after ASCT	Censored	Last evaluable disease assessment date prior to ASCT
Death due to disease progression (at any time)	Event	Death date
Death due to drug-related toxicity	Event	Death date
Non-disease related death (at any time)	Competing risk event	Death date
New anti-cancer therapy started before documented progression	Censored	Date of last evaluable disease assessment prior to initiation of new therapy
Progression or death documented after data cutoff for analysis	Censored	Date of last evaluable disease assessment prior to data cutoff for analysis
Withdrawal of consent or lost to follow-up prior to documented progression	Censored	Date of last evaluable disease assessment prior to data cutoff for analysis

12.4.2. Duration of response to retreatment (DORR): DORR is defined only for subjects who experience an objective response to retreatment and is the time from the first objective response after retreatment to disease progression after retreatment or death due to disease relapse. Non-disease related mortality will be modeled as a competing risk. Response and progression may be defined per Investigator read – Cheson, 2007 or Central Read – Cheson, 2007. Subjects not meeting the criteria for progression after retreatment or death due to disease relapse by the analysis data cutoff date will be censored at their last evaluable disease assessment date after retreatment. DORR will be derived using disease assessments obtained on study prior to initiation of new anticancer therapy (excluding ASCT). Disease assessments obtained after ASCT will be used in the derivation of DORR. A sensitivity analysis may be conducted in which disease assessments obtained after ASCT are not included in the derivation of DORR.

Primary analysis of DORR:

Circumstance	Event / Censored	Date of Event / Censoring
Progression per Cheson 2007 at a scheduled assessment or in between scheduled assessments and prior to initiation of new anticancer therapy (excluding ASCT)	Event	Progression date
Progression per Cheson 2007 at a scheduled assessment or in between scheduled assessments and after ASCT	Event	Progression date
Remain in response per Cheson 2007 at a scheduled assessment or in between scheduled assessments and after ASCT	Censored	Last evaluable disease assessment date
Death due to disease progression (at any time)	Event	Death date
Non-disease related death (at any time)	Competing risk event	Death date
Death due to drug-related toxicity	Event	Death date
New anti-cancer therapy started before documented progression	Censored	Date of last evaluable disease assessment prior to initiation of new therapy
Progression or death documented after data cutoff for analysis	Censored	Date of last evaluable disease assessment prior to data cutoff for analysis
Withdrawal of consent or lost to follow-up prior to documented progression	Censored	Date of last evaluable disease assessment prior to data cutoff for analysis

All references to progression in the table above refer to progression after retreatment.

Sensitivity analysis of DORR (censoring at ASCT):

Circumstance	Event / Censored	Date of Event / Censoring
Progression per Cheson 2007 at a scheduled assessment or in between scheduled assessments and prior to initiation of new anticancer therapy (excluding ASCT)	Event	Progression date
Progression per Cheson 2007 at a scheduled assessment or in between scheduled assessments and after ASCT	Censored	Last evaluable disease assessment date prior to ASCT
Remain in response per Cheson 2007 at a scheduled assessment or in between scheduled assessments and after ASCT	Censored	Last evaluable disease assessment date prior to ASCT
Death due to disease progression (at any time)	Event	Death date
Non-disease related death (at any time)	Competing risk event	Death date
Death due to drug-related toxicity	Event	Death date
New anti-cancer therapy started before documented progression	Censored	Date of last evaluable disease assessment prior to initiation of new therapy
Progression or death documented after data cutoff for analysis	Censored	Date of last evaluable disease assessment prior to data cutoff for analysis
Withdrawal of consent or lost to follow-up prior to documented progression	Censored	Date of last evaluable disease assessment prior to data cutoff for analysis

All references to progression in the table above refer to progression after retreatment.

12.4.3 Progression-free Survival (PFS): PFS is defined as the time from the KTE-C19 infusion date to the date of disease progression or death from any cause. Progression may be defined per Investigator read – Cheson, 2007 or Central Read – Cheson, 2007. Subjects not meeting the criteria for progression by the analysis data cutoff date will be censored at their last evaluable disease assessment date. PFS will be derived using disease assessments obtained on study prior to initiation of new anti-cancer therapy (excluding ASCT). Disease assessments after ASCT will be used in the derivation of PFS.

Primary analysis of PFS:

Circumstance	Event / Censored	Date of Event / Censoring
Progression per Cheson 2007 at a scheduled assessment or in between scheduled assessments and prior to initiation of new anticancer therapy (excluding ASCT)	Event	Progression date
Progression per Cheson 2007 at a scheduled assessment or in between scheduled assessments after ASCT	Event	Progression date
Remain in response per Cheson 2007 at a scheduled assessment or in between scheduled assessments after ASCT	Censored	Assessment date
Death (at any time) before documented progression	Event	Death date
New anti-cancer therapy started before documented progression	Censored	Date of last evaluable disease assessment prior to initiation of new therapy
Progression or death documented after data cutoff for analysis	Censored	Date of last evaluable disease assessment prior to data cutoff for analysis
Withdrawal of consent or lost to follow-up prior to documented progression	Censored	Date of last evaluable disease assessment prior to data cutoff for analysis
No disease assessment done by the cutoff date	Censored	KTE-C19 infusion date

12.4.4 Overall Survival (OS): OS is defined as the time from the KTE-C19 infusion to the date of death from any cause. Subjects who have not died by the analysis data cutoff date will be censored at their last date known to be alive prior to the data cutoff date with the exception that subjects known to be alive or determined to have died after the data cutoff date for each analysis will be censored at the data cutoff date.

Circumstance	Event / Censored	Date of Event / Censoring
Death before data cutoff date for analysis	Event	Date of death
Death after data cutoff date for analysis	Censored	Data cutoff date
Known to be alive after data cutoff date for analysis	Censored	Data cutoff date
Alive up through data cutoff date and no further information available after data cutoff date	Censored	last date known to be alive date up through the data cutoff date
Withdrawal of consent or lost to follow up prior to data cutoff date	Censored	Last date known to be alive prior to consent withdrawal or lost to follow up

12.4.5 Last date known to be alive

The last date known to be alive with be derived by obtaining the maximum complete date among the following data modules:

- Start date of AE (including targeted AE)
- Leukapheresis dates
- Conditioning chemo admin dates
- KTE-C19 infusion dates
- CT scan dates
- PET scan dates
- Clinical symptoms of lymphoma assessment dates
- Target lesion assessment
- Non-target lesion assessment
- New lesion assessment
- Disease response assessment
- Long term follow up subject status date where status = ‘alive’
- End of treatment disposition where status is not equal to death, lost to follow up
- End of post-treatment assessment period where status is not equal to death, lost to follow up
- End of study data where end of study reason is not equal to death, lost to follow up

Summary of Changes in KTE-C19-101 (ZUMA-1)

Statistical Analysis Plan (SAP)

SAP version 1.0 was dated 11 May 2015; version 2.0 was dated 28 Aug 2016. Version 2.0 included changes based on KTE-C19-101 Protocol Amendment 5 and other changes to the analyses as follows:

- Descriptions of sample size and statistical analyses of Cohort 3 were added.
- The overall estimated study population size across all cohorts (including Cohort 3) was increased, with a new estimate of 148 to 166 subjects.
- Details regarding the primary analyses of Phase 2 with respect to Cohorts 1, 2, and 3 were clarified.
- Additional covariates were added and prioritized for efficacy and or safety testing.
- Details concerning the statistical procedures for the IA1 futility analysis and the IA2 efficacy analysis were added.
- Details concerning the SCHOLAR-1 pooled analysis and the literature-based historical control were added or clarified.
- The study endpoints were modified to include identified and potential risks and axicabtagene ciloleucel (KTE-C19) product characteristics.
- The method for determining the subject's refractory subgroup at baseline was clarified.
- Methods for identifying CRS and neurotoxic events were added.
- Analyses involving competing risks and the calculation of DOR were clarified.
- An analysis of DOR stratified by ASCT after treatment with axicabtagene ciloleucel (KTE-C19) was added.
- The dose of axicabtagene ciloleucel (KTE-C19) required for a subject to be included in the mITT was clarified.
- The safety analysis set for interim analyses was defined as all subjects with at least 1 month of follow-up.
- Tocilizumab and steroids were added to the list of concomitant medications to be summarized.
- Allogenic SCT was added to the description of subsequent anti-cancer therapy.
- Incidence of allogeneic SCT after treatment with axicabtagene ciloleucel (KTE-C19) was added.
- Information regarding the study pause criteria for DSMB review was added.
- Specified AEs of interest; namely, identified risks (CRS, neurologic events, infections, and cytopenias, including febrile neutropenia) and potential risks (auto-immune disorders, secondary malignancies, tumor lysis syndrome, and immunogenicity) were clarified.

Protocol Title:	A Phase 1-2 Multi-Center Study Evaluating the Safety and Efficacy of KTE-C19 in Subjects with Refractory Aggressive Non-Hodgkin Lymphoma (NHL)
Protocol Number:	KTE-C19-101
Clinical Study Sponsor:	Kite Pharma, Inc. 2225 Colorado Avenue Santa Monica, CA 90404 United States of America
Key Sponsor Contacts:	**William Go, M.D., Ph.D.** Senior Director, Clinical Development Kite Pharma, Inc. 2225 Colorado Avenue Santa Monica, CA 90404 **Phone: 424.322.1934** **Email: wgo@kitepharma.com** Jeff Aycock Senior Director, Clinical Operations Kite Pharma, Inc. 2225 Colorado Avenue Santa Monica, CA 90404 Phone: 424.322.1935 Email: jaycock@kitepharma.com Allison Bowen MPM, PMP, BS, BA Theorem Clinical Research 1016 W. Ninth Avenue King of Prussia, PA 19406 Phone: 404.792.7824 Email: Allison.Bowen@TheoremClinical.com
Version:	**2.0 (Amendment #1)**
Date:	**January 20, 2015**

Investigators Agreement

I have read the attached protocol titled: A Phase 1-2 Multi-Center Study Evaluating the Safety and Efficacy of KTE-C19 in Subjects with Refractory Aggressive Non-Hodgkin Lymphoma (NHL) dated **January 20, 2015** and agree to abide by all provisions set forth therein.

I agree to comply with the International Conference on Harmonization Tripartite Guideline on Good Clinical Practice and applicable national or regional regulations and guidelines.

I agree and will ensure that financial disclosure statements will be completed by:

- Me (including, if applicable, my spouse, legal partner and dependent children)
- Sub-Investigators (including, if applicable their spouse, legal partner and dependent children)

at the start of the study and for up to one year after the study is completed.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the conduct of the clinical investigation without prior written consent from Kite Pharma Inc.

_____

Signature

_____

Name of investigator

_____

Date

Protocol Synopsis

Title

A Phase 1-2 Multi-Center Study Evaluating the Safety and Efficacy of KTE-C19 in Subjects with Refractory Aggressive Non-Hodgkin Lymphoma (NHL).

Indication

The indication is for the treatment of adult subjects with refractory diffuse large B cell lymphoma (DLBCL), **primary mediastinal B cell lymphoma (PMBCL) and transformed follicular lymphoma (TFL).**

Study Design

Study KTE-C19-101 is a phase 1-2 multicenter, open-label study evaluating the safety and efficacy of KTE-C19 in subjects with refractory aggressive NHL. The trial will be separated into two distinct phases designated as phase 1 and phase 2.

During phase 1, approximately 6-12 subjects with DLBCL, PMBCL or TFL will be enrolled to evaluate the safety of KTE-C19. If the regimen is safe based on the incidence of dose-limiting toxicity (DLT), phase 2 will open to enrollment. If the initial regimen is not safe, a lower dose of 1 x 10^6 Chimeric Antigen Receptor (CAR) positive (+) T cells/kg may be evaluated in an additional 6-12 subjects. A safety review team (SRT), internal to the study sponsor, will review the safety data and make recommendations on further study conduct of phase 1 as outlined in Section 9.6.

In phase 2, subjects will enroll into 2 separate cohorts designated as cohort 1 and cohort 2.

- Cohort 1 will enroll adult subjects with refractory DLBCL.
- Cohort 2 will enroll adult subjects with refractory PMBCL and TFL.
    - TFL is defined as subjects who received prior chemotherapy for follicular lymphoma

Independent of the phase of the study (phase 1 or phase 2) or which cohort (cohort 1 or cohort 2 of phase 2 only) each subject will follow the same study treatment schedule and procedural requirements. Each subject will proceed through the following study periods:

- Screening/leukapheresis period
- Conditioning chemotherapy period
- Investigational Product (IP) treatment period
- Post treatment assessment period
- Long term follow-up period

For study requirements assigned to each study period, please refer to Section 7 for details.

Study Objectives

The primary objective of phase 1 is to evaluate the safety of KTE-C19.

The primary objective of phase 2 is to evaluate the efficacy of KTE-C19, as measured by objective response rate in subjects with DLBCL, PMBCL, and TFL. Secondary objectives will include assessing the safety and tolerability of KTE-C19 and additional efficacy endpoints.

Hypothesis

This study is designed to differentiate between a treatment that has a true response rate of 20% or less and a treatment with a true response rate of 40% or more. The hypothesis is that the objective response rate to KTE-C19 in the DLBCL cohort and in the overall study population is significantly greater than 20%.

Primary Endpoint

- Phase 1: Incidence of adverse events defined as dose-limiting toxicities (DLT)
- Phase 2: Objective response rate (complete response [CR] + partial response [PR]) per the revised International Working Group (IWG) Response Criteria for Malignant Lymphoma (Cheson 2007).

Secondary Endpoint(s) for phase 1 and 2

- Objective response rate (CR + PR) per the revised IWG Response Criteria for Malignant Lymphoma (Cheson 2007). (phase 1 portion)
- Duration of Response
- Progression Free Survival
- Overall Survival
- Incidence of adverse events and clinical significant changes in safety lab values
- Incidence of anti-KTE-C19 antibodies
- Levels of anti-CD19 CAR+ T cells in blood
- Levels of cytokines in serum

Exploratory Endpoint(s) for phase 1 and 2

- Objective response rate (CR + PR) per revised IWG Response Criteria for Malignant Lymphoma (Cheson 2007) and duration of second response among subjects retreated with KTE-C19
- **Investigation of potential biomarker development based on assessment of blood cells, tumor cells and the proposed actions of the investigational product**

Sample Size

Approximately 118-124 subjects

Phase 1: approximately 6-12 subjects

Phase 2: approximately 112 subjects enrolled into 2 cohorts

- Cohort 1: Approximately 72 subjects
- Cohort 2: Up to 40 subjects

Study Eligibility

Please refer to Section 5 for a complete and detailed list of inclusion and exclusion criteria for both phases of the study.

Treatment

Investigational Product:

- KTE-C19 treatment consists of a single infusion of CAR transduced autologous T cells administered intravenously at a target dose of 2 x 10^6 anti-CD19 CAR+ T cells/kg (± 20%; 1.6 x 10^6 anti-CD19 CAR+ T cells/kg to 2.4 x 10^6 anti-CD19 CAR+ T cells/kg). Under circumstances where subjects initially respond and subsequently relapse, subjects may be eligible for a second course of conditioning chemotherapy and KTE-C19. Refer to Section 6 for treatment details.

Conditioning Chemotherapy Treatment:

- KTE-C19 is administered after a conditioning chemotherapy regimen consisting of fludarabine 30 mg/m^2/day and cyclophosphamide 300 mg/m^2/day, administered x 3 days. Refer to Section 6 for chemotherapy treatment details.

Independent of the phase of the study (phase 1 or phase 2) or which cohort (cohort 1 or cohort 2 of phase 2 only) each subject will follow the same study treatment schedule and procedural requirements.

Procedures

At specific time points as outlined in the schedule of assessments, subjects will undergo the following procedures: collection of informed consent, general medical history including previous treatments for NHL, physical exam including vital signs and performance status, neurocognitive assessments, urinalysis, blood draws for complete blood count (CBC), chemistry panels, cytokines, lymphocyte subsets, anti-KTE-C19 antibodies, replication competent retrovirus (RCR) and anti-CD19 CAR+ T cell analysis. Women of child-bearing potential will undergo a urine or serum pregnancy test.

Subjects will also undergo a baseline electrocardiogram (ECG), echocardiogram (ECHO), brain magnetic resonance image (MRI), a positron emission tomography–computed tomography (PET-CT), and leukapheresis.

Routinely throughout the conduct of the study, subjects will be asked to report concomitant medications and adverse events and will have their disease assessed.

Safety Review Team and Data Safety Monitoring Board

A SRT, that is internal to the study sponsor and in collaboration with at least one study investigator, will review safety data in phase 1 of the study. The SRT will be chartered to make a recommendation to progress the study from phase 1 to phase 2 based on review the incidence of KTE-C19 DLT and serious adverse events. For details surrounding the SRT and DLT criteria, refer to Section 9.6.

An independent Data Safety Monitoring Board (DSMB) will meet 2 times during the phase 2 portion of the study when 20 and 50 subjects enrolled into cohort 1 have completed their 3 month disease assessment. The DSMB will review safety and efficacy data and be chartered to make trial conduct recommendations based on an analysis of risk vs. benefit. The DSMB may meet more often as needed. For details surrounding the DSMB, refer to Section 9.7.

Statistical Considerations

The primary endpoint for the phase 1 portion of the study is the incidence of DLT.

The primary endpoint for the phase 2 portion of the study is objective response rate per the revised IWG Response Criteria for Malignant Lymphoma (Cheson 2007). This endpoint will be based on a modified intent to treat (mITT) population consisting of all subjects who receive the planned **dose** of KTE-C19.

This study uses a single-arm design to test for an improvement in response rate in the DLBCL cohort (n=72) and in the overall study population (cohorts 1 and 2 combined; n=112). For the test of efficacy this study has ≥ 90% power to distinguish between an active therapy with a 40% true response rate from a therapy with a response rate of 20% or less with a 1-sided alpha level of 0.025.

The overall 1-sided alpha level of 0.025 will be divided between the inference on cohort 1 and the inference in the overall study population using the methodology described in Song (2007) and Wang (2007) with pre-specification of the cohort 1 subgroup and overall study population testing as described in Moye (2001). The objective response for cohort 1 will be tested at a 1-sided alpha level of 0.022 and the objective response rate in the overall study population will be tested at a 1-sided alpha level of 0.0075.

Within cohort 1, 2 interim and 1 primary analyses will be performed.

- Interim analysis 1 will be conducted after 20 subjects in the mITT set have been evaluated for response 3 months after the KTE-C19 infusion. This interim analysis will be for futility only.
- Interim analysis 2 will be conducted after 50 subjects have been evaluated for response 3 months after the KTE-C19 infusion. This interim analysis will assess early demonstration of efficacy.
- The primary analysis of cohort 1 will occur after all subjects in cohort 1 have been assessed for response 6 months after the KTE-C19 infusion.

An alpha spending function will be used to allocate the alpha level for the test of cohort 1 between interim analysis 2 of cohort 1 and the primary analysis of cohort 1. Inferential analyses of the overall study population (including cohort 2) will not be performed at interim analysis 1 or 2 of cohort 1. Accrual to the study will continue during interim analysis 1 and interim analysis 2 of cohort 1.

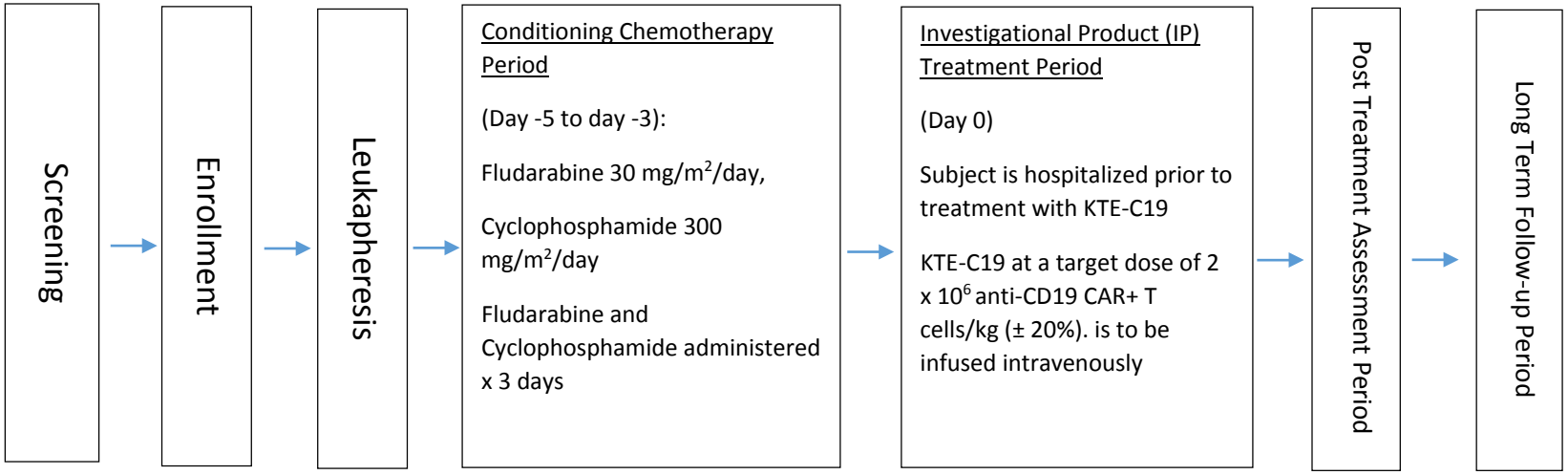
Within the overall study population, 1 primary analysis will be performed when all subjects accrued to cohorts 1 and 2 have been assessed for response 6 months after the KTE-C19 infusion.

Study Glossary

Abbreviation or Term	Definition/Explanation
AE	adverse event
ANC	absolute neutrophil count
ASCT	autologous stem cell transplant
CAR	chimeric antigen receptor
CAR+	chimeric antigen receptor positive
CBC	complete blood count
CLL	chronic lymphocytic leukemia
CNS	central nervous system
CPF	central processing facility
CR	complete response
CRF	case report form
CRS	cytokine release syndrome
CSF	cerebrospinal fluid
CTCAE	common terminology criteria for adverse events
DLBCL	diffuse large B cell lymphoma
DLT	dose-limiting toxicity
DSMB	data safety monitoring board
eACT™	engineered autologous cell therapy
EBV	epstein-Barr virus
ECHO	Echocardiogram
ECG	Electrocardiogram
ECOG	eastern cooperative oncology group
End of Study for individual subject	Defined as when the last day that protocol specified assessments are conducted for an individual subject
End of Study (primary completion)	Defined as when the last subject is assessed or received an intervention for the purposes of final collection of data for the primary endpoint at Month 6
End of Study (end of trial)	Defined as when the last subject is assessed or received an intervention for evaluation in the study, including survival assessments
FL	follicular lymphoma

HABA	human anti-bovine antibodies
HAMA	human anti-mouse antibodies
ICF	informed consent form
IP	investigational product
IRB/IEC	institutional review board/independent ethics committee
IWG	International working group
KTE-C19	autologous T cells transduced with retroviral vector containing anti-CD19 CD28/CD3 zeta chimeric antigen receptor
LTFU	long term follow-up
mITT	modified intend to treat
MMSE	mini mental status exam
MRI	magnetic resonance imaging
NCI	National Cancer Institute
NHL	non-hodgkin lymphoma
OS	overall survival
PET-CT	positron emission tomography–computed tomography
PBMC	peripheral blood mononuclear cells
PMBCL	primary mediastinal B cell lymphoma
PD	progressive disease
PR	partial response
RCR	replication competent retrovirus
scFv	single chain variable fragment
SOA	schedule of assessments
SD	stable disease
SRT	safety review team
Study day 0	Defined as the first day that KTE-C19 is administered to the subject
TEAEs	treatment emergent adverse events
TFL	transformed follicular lymphoma

Study Schema (Phase 1 and Phase 2):



Study KTE-C19-101 is a phase 1-2 single-arm, open-label, multicenter study evaluating the safety and efficacy of KTE-C19 in subjects with refractory DLBCL, PMBCL and TFL.

During phase 1, approximately 6-12 subjects will be enrolled to evaluate the safety of KTE-C19. If the regimen is safe based on the incidence of dose-limiting toxicity (DLT), phase 2 will open to enrollment. If the initial regimen is not safe, a lower dose of 1 x 10^6 anti-CD19 CAR+ T cells/kg may be evaluated in an additional 6-12 subjects. A safety review team (SRT) will review the safety data and make recommendations on further study conduct of phase 1 as outlined in Section 9.6.

Upon SRT recommendation, phase 2 will commence and enroll subjects into 2 separate cohorts designated as cohort 1 and cohort 2.

- Cohort 1 will enroll adult subjects with refractory DLBCL.
- Cohort 2 will enroll adult subjects with refractory PMBCL & TFL. Refer to entrance criteria for TFL eligibility requirements.

Independent of the phase of the study (phase 1 or phase 2) or which cohort (cohort 1 or cohort 2 of phase 2 only) each subject will follow the same study treatment schedule and procedural requirements. Each subject will follow through the following study periods: a screening/leukapheresis period, a conditioning chemotherapy period, an IP treatment period, a post treatment assessment period and a long term follow-up period.

Table of Contents

Tables and Figures

1 Objectives

The primary objective of phase 1 is to evaluate the safety of KTE-C19.

The primary objective of phase 2 is to evaluate the efficacy of KTE-C19, as measured by objective response rate in subjects with DLBCL, PMBCL, and TFL. Secondary objectives will include assessing the safety and tolerability of KTE-C19 and additional efficacy endpoints.

2 Disease Background and Rationale

Non-Hodgkin lymphoma (NHL) is a heterogeneous group of cancers originating in B lymphocytes, T lymphocytes or natural killer cells. In the United States, B cell lymphomas represent 80-85% of cases reported. In 2013 approximately 69,740 new cases of NHL and over 19,000 deaths related to the disease were estimated to occur. Non-Hodgkin lymphoma is the most prevalent hematological malignancy and is the seventh leading site of new cancers among men and women and account for 4% of all new cancer cases and 3% of deaths related to cancer (SEER 2014).

2.1 Diffuse Large B cell Lymphoma

Diffuse large B cell lymphoma (DLBCL) is the most common subtype of NHL, accounting for approximately 30% of NHL cases. There are approximately 22,000 new diagnoses of DLBCL in the United States each year. It is classified as an aggressive lymphoma with the majority of patients cured with conventional chemotherapy (NCCN guidelines NHL 2014).

First line therapy for DLBCL typically includes an anthracycline-containing regimen with rituximab. The first line objective response rate and the complete response (CR) rate to RCHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) is approximately 80% and 50% respectively (Coiffier 2002). Long term follow-up of the GELA LNH-98.5 study demonstrated a 5 year overall survival (OS) of 58% and a 10 year OS of 42% with this regimen (Coiffier 2009). However, approximately one-third of patients have refractory disease to initial therapy or relapse after RCHOP (Sehn 2005).

For those patients who relapse after response to first line therapy, approximately 40-60% of patients can achieve a second response with additional chemotherapy. For patients who are young and fit, the goal of second line therapy is to achieve a response that will make the patient eligible for autologous stem cell transplant (ASCT). The standard of care for second-line therapy for transplant-eligible patients includes rituximab and combination chemotherapy such as RICE (rituximab, ifosfamide, carboplatin, and etoposide) and RDHAP (rituximab, dexamethasone, cytarabine, and cisplatin). In a large randomized trial of RICE versus RDHAP in transplant-eligible patients with DLBCL (the CORAL study) 63% of patients achieved an objective response to either regimen with a 26% CR rate (Gisselbrecht 2010).

Patients who respond to second line therapy and who are considered fit enough for transplant receive consolidation with high-dose chemotherapy and ASCT. This combination is curative in about half of transplanted patients (Gisselbrecht 2010). A major predictor of outcome after ASCT is the patient's response to second line chemotherapy; patients who achieve a CR to second-line therapy have the highest chance of cure, while patients who achieve only partial response (PR) or stable disease have a low rate of successful transplant (Armandi 2013).

Patients who failed ASCT have a very poor prognosis and no curative options. A retrospective analysis of 56 patients with DLBCL with prior exposure to rituximab who had disease progression following ASCT was performed. Their median OS from progression following ASCT was 9.9 months (95% CI: 5.3–13.1 months). The 45 patients who progressed less than a year after their ASCT had a median OS of 8.2 months (Nagle 2013).

The majority of second line patients are not eligible for ASCT due to chemotherapy-refractory disease, age, or comorbidities such as heart, lung, liver, or kidney disease. Transplant-ineligible salvage patients do not have a curative option available to them.

There is no standard definition of relapsed/refractory DLBCL. Table 1 illustrates that no matter which criterion is used, the DLBCL population with the more refractory disease demonstrates a lower response rate.

Table 1. Objective response rate by criteria based on best response and/or length of response to previous chemotherapy regimen

Trial	Treatment	Criteria	N	ORR
Philip 1995 (PARMA)	DHAP[1]	Relapsed following first line after initial CR	187	64%
		Relapsed during first line therapy after initial CR	28	21%
Gisselbrecht 2010 (CORAL)	Rituximab + ICE[2] or DHAP	Relapsed > 12 months after diagnosis	160	88%
		Relapsed < 12 months after diagnosis	228	46%
Fayad 2013 (Phase 2)	Rituximab + Inotuzumab-Ozogamicin	Response to prior therapy: CR/CRu	28	82%
		Response to prior therapy: PR/SD	17	47%
		Response to prior therapy: PD	21	19%
Matasar 2013	Ofatumumab + ICE or DHAP	Relapsed > 12 months	12	83%
		CR <12 months, PR, SD, PD, or unknown with PFS <12 months	47	55%
		Primary progressive disease on RCHOP	10	10%

[1] DHAP: dexamethasone, cytarabine, and cisplatin. [2] ICE: ifosfamide, carboplatin, and etoposide

The population with highest unmet need continues to consist of patients that do not respond to first line combination chemotherapy (typically R-CHOP) or do not respond to their last course of combination chemotherapy, as the disease is mostly insensitive to subsequent combination chemotherapy (typically R-ICE, R-ESHAP). In a review of 64 patients with DLBCL with disease progression during first line chemotherapy or only transient response (≤90 days) after end of induction treatment, the response rate to second line therapy was 15% and the median OS was 6.8 months, and no patient survived more than 26 months after first diagnosis (Josting 2000). An analysis of outcome in 1126 patients with DLBCL after first line RCHOP included 33 patients with primary refractory DLBCL who received second line therapy with curative intent. Only 3 (9%) were able to receive ASCT, and only 1 (3%) patient achieved long term survival (Hitz 2010). Seshadri et al analyzed 120 patients who did not respond to second line platinum-based chemotherapy regimens (e.g. R-ICE) and showed that only 14% responded to their third line therapy (Seshadri 2008). Ardeshna et al. followed 19 patients with aggressive NHL, and 9 patients with

transformed follicular lymphoma that did not respond to second line chemotherapy. Only 5 of the 28 total patients (18%) responded to third line chemotherapy (Ardeshna 2005).

These consistently discouraging results demonstrate that new treatment options are urgently needed for patients whose tumors have demonstrated a lack of response to chemotherapy.

This trial will enroll patients with chemo-refractory lymphoma, as evidenced by failure to achieve even a transient or partial response to prior biologic and combination chemotherapy or by early recurrence after ASCT.

2.2 Primary Mediastinal B Cell Lymphoma and Transformed Follicular Lymphoma

Primary mediastinal B cell lymphoma (PMBCL) has distinct clinical, pathological, and molecular characteristics compared to DLBCL. PMBCL is thought to arise from thymic (medullary) B cells and represents approximately 3% of patients diagnosed with DLBCL. PMBCL is typically identified in the younger adult population in the fourth decade of life with a slight female predominance (Sehn 1998, Savage 2006). Gene expression profiling suggests deregulated pathways in PMBCL overlap with Hodgkin lymphoma. Initial therapy of PMBCL generally includes anthracycline-containing regimens with rituximab with or without involved field radiotherapy. A recent phase 2, prospective study of infusional dose-adjusted etoposide, doxorubicin, and cyclophosphamide with vincristine, prednisone, and rituximab (DA-EPOCH-R) demonstrated radiotherapy may not be required (Dunleavy 2013).

Follicular lymphoma (FL), a B cell lymphoma, is the most common indolent (slow-growing) form of NHL, accounting for approximately 20% to 30% of all NHLs. Some patients with FL will transform (TFL) histologically to DLBCL which is more aggressive and associated with a poor outcome. Histological transformation to DLBCL occurs at an annual rate of approximately 3% for 15 years with the risk of transformation continuing to drop in subsequent years. The biologic mechanism of histologic transformation is unknown. Initial treatment of TFL is influenced by prior therapies for follicular lymphoma but generally includes anthracycline-containing regimens with rituximab to eliminate the aggressive component of the disease (NCCN practice guidelines 2014).

Treatment options for relapsed/refractory PMBCL and TFL are similar to those in DLBCL. Given the low prevalence of these diseases, no large prospective randomized studies in these patient populations have been conducted. Patients with chemotherapy refractory disease have a similar or worse prognosis (Kuruvilla 2008) to those with refractory DLBCL.

In summary, subjects who have refractory, aggressive NHL (e.g. DLBCL, PMBCL and TFL) have a major unmet medical need and further research with novel treatments are warranted in these populations.

2.3 Study Rationale

As most advanced cancers eventually become refractory to conventional therapies, new treatment modalities are needed. Immunotherapy, which is based on the enhancement of an immune response against the tumor, is a promising approach to treating many cancer types. T cells play an important role in destroying diseased cells throughout the body. Studies with immune checkpoint inhibitors and tumor infiltrating lymphocytes have demonstrated the potential of T cells to treat cancer. T cells need to possess the appropriate specificity for a tumor, be present in sufficient numbers, and overcome any local immunosuppressive factors to be effective. Engineered T cells are a promising approach for cancer therapy (Kershaw 2013).

Engineered Autologous Cell Therapy (eACT™) is a process by which a patient's own T cells are collected and subsequently genetically altered to recognize and target antigens expressed on the cell surface of specific malignancies (Kochenderfer 2013). The ability to genetically engineer human T cells and use them to mediate cancer regression in patients has been demonstrated in a number of studies and has opened possibilities for the treatment of patients with a wide variety of cancer types including B cell malignancies expressing the CD19 antigen.

2.3.1 CD19 and Expression

CD19 is a 95 kD transmembrane protein expressed only in the B cell lineage. It is expressed in all normal B cells starting at the pre-B cell stage until the final differentiation stage and is not expressed in pluripotent hematopoietic stem cells or most plasma cells. The pattern of CD19 expression is maintained in B cell malignancies including all subtypes of B cell NHL, chronic lymphocytic leukemia (CLL), and non T cell acute lymphoblastic leukemia (ALL) (Blanc 2011) with the exception of multiple myeloma.

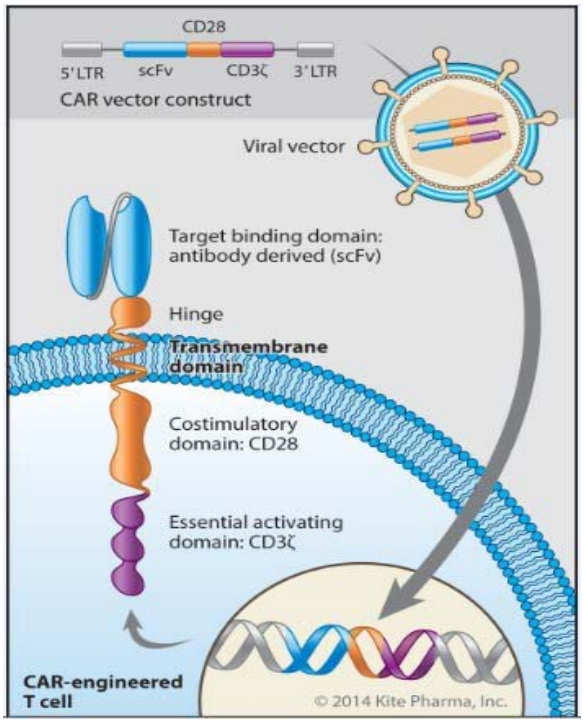
2.3.2 Anti-CD19 CAR+ T cell Product

Anti-CD19 chimeric antigen receptor (CAR) positive (+) T cells are autologous human T cells that have been engineered to express an extracellular single chain variable fragment (scFv) with specificity for CD19 linked to an intracellular signaling part comprised of signaling domains from CD28 and CD3ζ (CD3-zeta) molecules arranged in tandem.

An anti-CD19 CAR vector construct has been designed, optimized and initially tested at the Surgery Branch of the National Cancer Institute (NCI) (Figure 1; Kochenderfer 2009, 2010a). The scFv is derived from the variable region of the anti-CD19 monoclonal antibody FMC63 (Nicholson 1997). A portion of the CD28 costimulatory molecule is added, as murine models suggest this is important for the anti-tumor effect and persistence of anti-CD19 CAR+ T cells (Kowolik 2006). The signaling domain of the CD3-zeta chain is essential for T cell activation. These fragments were cloned into the murine stem cell virus-based (MSGV1) vector, utilized to genetically engineer the autologous T cells. Treatment with anti-CD19 CAR+ T cells is currently being administered to subjects with CD19+ B cell malignancies in ongoing NCI protocol 09-C-0082. The same CAR vector construct will be used in this study.

The CAR construct is inserted into the T cells' genome by retroviral vector transduction. Briefly, peripheral blood mononuclear cells (PBMCs) are obtained by leukapheresis and Ficoll separation. PBMCs are activated by culturing with an anti-CD3 antibody in the presence of **recombinant** IL-2. Stimulated cells are transduced with a retroviral vector containing an anti-CD19 CAR gene and propagated in culture to generate sufficient engineered T cells for administration. The NCI production process has been modified to create a closed, efficient process for this clinical trial.

Figure 1. Anti-CD19 Chimeric Antigen Receptor



2.3.3 Anti-CD19 CAR+ T cell Study Results

Study Design

The NCI study was designed as a phase 1/2, single arm, open label, trial of anti-CD19 CAR+ T cells in subjects with relapsed/refractory B cell malignancies. The primary objective of the study was to determine the safety and feasibility of anti-CD19 CAR+ T cells administered to subjects with B cell malignancies.

Subjects who signed informed consent and met study eligibility were enrolled into the study and underwent leukapheresis to obtain PBMCs for the production of anti-CD19 CAR+ T cells. Subjects were treated with conditioning chemotherapy prior to hospitalization in preparation for a single infusion of anti-CD19 CAR+ T cells on Day 0. Some subjects were then treated with interleukin-2 (Group 1 only), 3 hours after the anti-CD19 CAR+ T cell infusion. Retreatment of a second dose of anti-CD19 CAR+ T cells was allowed if there was a response of PR or CR after the first infusion and then subsequent disease progression.

The protocol was originally designed as a dose escalation study, but as a result of DLTs, the protocol has been amended several times in an effort to reduce toxicity. As the study proceeded, three groups of subjects have been enrolled:

Group 1 consisted of 8 subjects, including 1 subject who was retreated, dosed with anti-CD19 CAR+ T cells ranging from 3 x 10^6 through 30 x 10^6 anti-CD19 CAR+ T cells/kg. The dose of anti-CD19 CAR+ T cells followed a conditioning regimen consisting of high dose cyclophosphamide (60-120 mg/kg) for two days followed by fludarabine (25 mg/m^2) for five days. These subjects also received high dose interleukin-2 (IL-2) (720,000 IU/kg every 8 hours until 15 doses or toxicity precluded additional doses) after the anti-CD19 CAR+ T cell administration to stimulate their proliferation.

Group 2 consisted of 15 subjects, including 2 subjects from Group 1 who were retreated, who received high dose cyclophosphamide and fludarabine and no interleukin-2 following varying doses of anti-CD19 CAR+ T cell administration (1 x 10^6 through 5 x 10^6 anti-CD19 CAR+ T cells/kg).

Group 3, as of August 31, 2014, has enrolled 9 subjects, who have received a reduced conditioning regimen of cyclophosphamide (300 mg/m^2) and fludarabine (30 mg/m^2), both given for 3 concurrent days with no IL-2. The first 7 and last 2 of these subjects received an anti-CD19 CAR+ T cell infusion of 1 x 10^6 anti-CD19 CAR+ T cells and 2 x 10^6 anti-CD19 CAR+ T cells, respectively.

Demographics

As of August 31, 2014, subject demographic and disease characteristics are provided in Table 2. Thirty (30) subjects were enrolled, 17 subjects (56.6%) had DLBCL or PMBCL, 7 subjects (23%) had CLL, and 6 subjects (20%) had other indolent NHL, including indolent follicular lymphoma and splenic marginal zone lymphoma. Most subjects had refractory disease (77%), and had received a median of 3 prior lines of therapy. All subjects with aggressive NHL received prior anti-CD20 therapy, platinum combination chemotherapy, and 93% received prior anthracycline-based chemotherapy (Data on file, Kite Pharma).

Table 2. Demographics

	Group 1 (N = 8)	Group 2 (N = 15)	Group 3 (N = 9)	Total (N = 30)
Age (years)				
Mean (std)	56 (6)	62 (11)	50 (17)	52 (12)
Median	56	55	55	55
Minimum, maximum	47, 63	31, 69	29, 67	27, 69
Gender				
Male	8 (100%)	8 (53%)	9 (100%)	23 (77%)
Female	0 (0%)	7 (46%)	0 (0%)	7 (23%)
Race				
White	8 (100%)	13 (87%)	8 (89%)	27 (90%)
Asian	0 (0%)	1 (7%)	0 (0%)	1 (3%)
Black or African American	0 (0%)	1 (7%)	0 (0%)	1 (3%)
Unknown	0 (0%)	0 (0%)	1 (11%)	1 (3%)
Diagnosis				
CLL	4 (50%)	4 (27%)	0 (0%)	7 (23%)
FL	3 (38%)	0 (0%)	1 (11%)	4 (13%)
SMZL	1 (13%)	1 (7%)	0 (0%)	1 (3%)
iNHL	0 (0%)	1 (7%)	0 (0%)	1 (3%)
DLBCL	0 (0%)	5 (33%)	7 (78%)	12 (40%)
PMBCL	0 (0%)	4 (27%)	1 (11%)	5 (17%)
Prior anti-CD20	7 (88%)	13 (87%)	9 (100%)	28 (93%)
Refractory to last line of therapy (SD/PD to last line)				
Yes	6 (75%)	12 (80%)	6 (67%)	23 (77%)
No	1 (13%)	2 (13%)	0 (0%)	2 (7%)
Unknown	1 (13%)	1 (7%)	3 (33%)	5 (17%)
Lines of prior therapy				
Median (minimum, maximum)	4 (2, 7)	3 (1, 12)	3 (2, 10)	3 (1, 12)

Derived from:
S:\CD19\Clinical Development\data\31AUG2014\TFLs from clinipace\IBTable1.rtf
S:\CD19\Clinical Development\data\31AUG2014\TFLs from clinipace\IBTable1_G1.rtf
S:\CD19\Clinical Development\data\31AUG2014\TFLs from clinipace\IBTable1_G2.rtf
S:\CD19\Clinical Development\data\31AUG2014\TFLs from clinipace\IBTable1_G3.rtf

Pharmacokinetics

The number of anti-CD19 CAR+ T cells in the peripheral blood at various time points after initial administration on Day 0 were evaluated using qPCR analysis and corroborated by standard curves generated by flow cytometry with an antibody reagent specific for scFv present in the anti-CD19 CAR construct (Kochenderfer 2012).

In group 1, 3 x 10^6 to 30 x 10^6 anti-CD19 CAR+ T cells/kg were infused. In the first 6 subjects, the anti-CD19 CAR+ T cells in blood circulation were detected at higher levels within 2 weeks after infusion, reaching up to 0.02-1% of total PBMC, then decayed rapidly and were undetectable after 50 days. Subjects 7 and 8, dosed with the highest number of anti-CD19 CAR+ T cells (28 and 30 x 10^6 anti-CD19 CAR+ T cells/kg, respectively), had higher peak percentages reaching >10% anti-CD19 CAR+ T cells of total PBMC, and longer-term persistence of anti-CD19 CAR+ T cells in blood (>130 and 180 days, respectively).

In group 2, in the absence of interleukin-2 treatment, the anti-CD19 CAR+ T cells showed a similar expansion in the peripheral blood within 2 weeks, followed by decay and complete disappearance from circulation within several weeks (Table 3).

Overall, there was no overt relationship between the dose of anti-CD19 CAR+ T cells and their expansion and persistence in the peripheral blood. Likewise, to date, there was no apparent relationship between the anti-CD19 CAR+ T cell dose, the anti-CD19 CAR+ T cell expansion or persistence in the blood, and the clinical response or the toxicities related to this therapy, respectively.

In groups 1 and 2, there was no secondary expansion of anti-CD19 CAR+ T cells following their primary expansion at 7-14 days post-infusion. There is no evidence of oncogenic transformation ascribable to the genomic insertion of the CAR-expression retrovirus in the subjects tested to date. Group 3 results were not yet available at the time of data cutoff.

Table 3. Anti-CD19 CAR+ T cell expansion and persistence in the peripheral blood of subjects in group 2

	Total dose of anti-CD19 CAR+ T cells (x 10^6)	Dose range of anti-CD19 CAR+ T cells/kg in millions (x 10^6)	Anti-CD19 CAR+ T cell peak – expressed as number of cells /ul blood	Time to peak in days	Persistence of anti-CD19 CAR+ T cells in days
Mean (Range)	210 (105-490)	3.1 (1.2-7.5)	50 (9-777)	10 (7-17)	32 (13-132)

Efficacy

As of August 31, 2014, 30 subjects had been evaluated for safety and 26 subjects had been evaluated for efficacy. The overall response rate for the 26 subjects evaluable for efficacy was 81%. Eleven (11) of 26 subjects (42%) achieved a CR and 10/26 subjects (38%) achieved a PR (Figure 2).

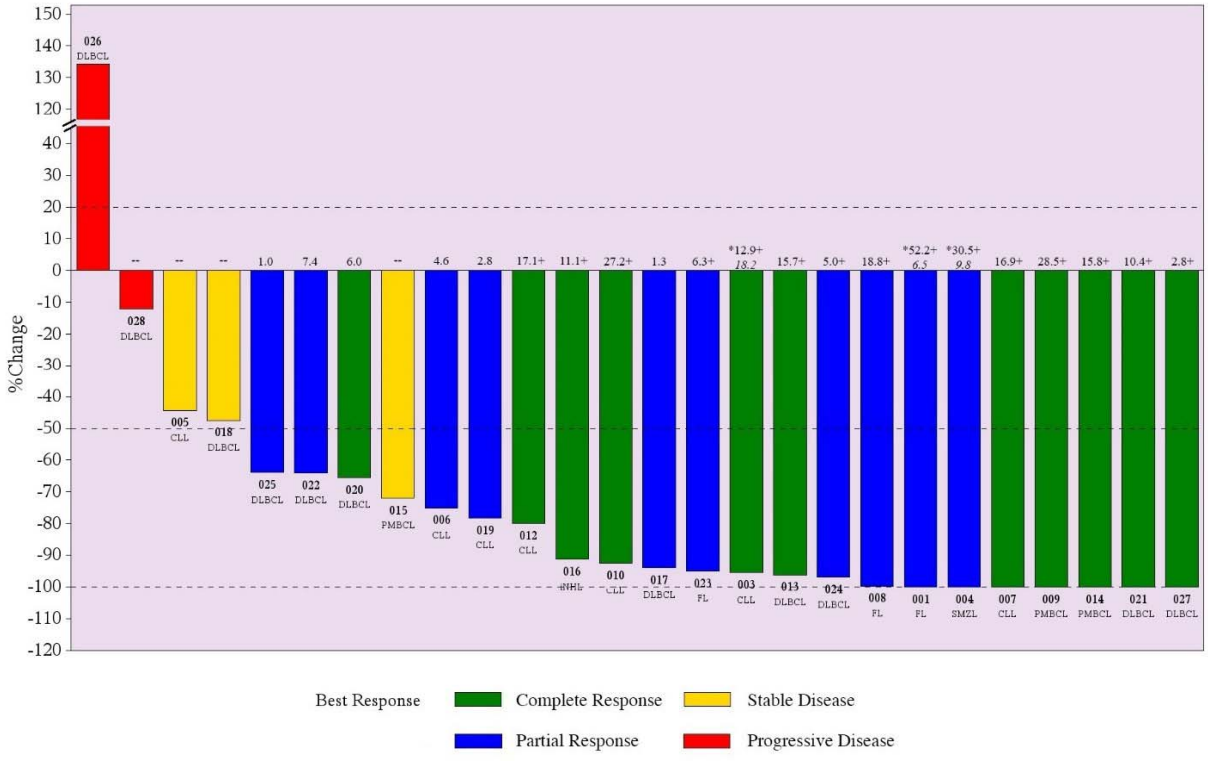
Fifteen of the 26 evaluable subjects remain in response from their first treatment, with 11 subject's (including retreated subjects) duration of response exceeding 1 year. Three responding subjects were retreated after progression, all have ongoing responses (12.9 to over 52.2 months) (Figure 2).

As indicated in Table 4, 14 of the 17 subjects with refractory aggressive DLBCL/PMBCL were evaluable for disease response (one was not evaluable; 2 had not yet been evaluated). Among these 14 subjects, 10 (71%) had a response with 6/14 subjects (43%) achieving a CR. The median duration of response is 6.7 months.

Six of the 7 subjects (86%) with CLL had a response with 4/7 subjects (57%) achieving a CR. The median duration of response is 17 months with 4/7 subjects (57%) still in response including 2 subjects with ongoing responses for greater than 27 months.

Five of the 5 subjects (100%) with indolent NHL had a response with 1/5 subjects (20%) achieving a CR. The median duration of response is 18.8 months. Five subjects (5/5; 100%) remain in response with 2 subjects responding greater than 40 months.

Figure 2. Best response to anti-CD19 CAR+ T cells in B cell malignancies



Subject 1010015 experienced a 72% reduction in tumor burden approximately 1 month after the anti-CD19 CAR infusion. This reduction was not confirmed in a follow up disease assessment 4 weeks later and the subject's best response was noted as stable disease.
*Denotes duration of response following subjects re-treatment - Lower number provides duration of response following initial anti-CD19 CAR infusion
Derived from: S:\CD19\Clinical Development\data\31AUG2014\TFLs from clinipace\corrected waterfall pt 23 FL.rtf

Table 4. Objective Response Rate and Duration of Response by Tumor Type

Tumor Type (n evaluable)	Overall Response Rate n (%)	Complete Response Rate n (%)	Duration of Response Median (Individual)
Any (n=26)	21 (81%)	11 (42%)	11.1
DLBCL/PMBCL (n=14)	10 (71%)	6 (43%)	6.7 (1, 1.3, 2.8+, 5.0+, 6.1, 7.4, 10.4+, 15.7+, 15.8+, 28.5+)
CLL (n=7)	6 (86%)	4 (57%)	17 (2.8, 4.6, 16.9+, 17.1+, 27.2+, 31.1+)
Indolent NHL (n=5)	5 (100%)	1 (20%)	18.8 (6.3+, 11.1+, 18.8+, 40.3+, 58.7+)

"+" indicates that the response is still ongoing

Derived from: S:\CD19\Clinical Development\data\31AUG2014\derived\derived efficacy data 31AUG2014.xls

Safety

Adverse Events

In NCI Protocol 09-C-0082, all CTCAE v3.0 grade 3-5 adverse events and grade ≥ 2 unexpected events were to be reported in the study database. Adverse events that occur after the start of the conditioning regimen are considered treatment-emergent. At the time of the 31 August 2014 data cutoff, 30 subjects had been treated with the anti-CD19 CAR+ T cells with no adverse events yet reported for the last subject treated. Overall safety summaries include all 30 treated subjects. Summaries by group include safety data for subjects 1010003 and 1010004 twice, once when these subjects were treated in Group 1 and second when these subjects were treated in Group 2 (retreatment with anti-CD19 CAR+ T cells).

Summary of Adverse Events

A summary of adverse events is provided in Table 5. Overall, 29 subjects (96.7%) experienced any adverse event, with 1 subject (3.3%) experiencing a worst grade of grade 3, 26 subjects (86.7%) experiencing a worst grade of grade 4, and 2 subjects (6.7%) with fatal adverse events. Eighteen subjects (60.0%) experienced an anti-CD19 CAR+ T cell related adverse event; 5 subjects (16.7%) worst grade of 3, 8 subjects (26.7%) worst grade 4, and no subjects experienced a grade 5 event. Sixteen subjects (53.3%) experienced a serious adverse event; 3 subjects (10%) worst grade of 3, 9 subjects (30%) worst grade of 4, and 2 subjects (6.7%) worst grade of 5.

Table 5. Summary of Adverse Events

	Group 1 (N=8)	Group 2 (N=15)	Group 3 (N = 9)	Overall (N=30)
n (%)				
Any Gr 2-5 AE Gr 3 Gr 4 Gr 5	8 (100) 0 (0) 7 (87.5%) 1 (12.5%)	15 (100) 0 (0) 14 (93.3%) 1 (6.7%)	8 (88.9) 1 (11.1) 7 (77.8) 0 (0)	29 (96.7%) 1 (3.3%) 26 (86.7%) 2 (6.7%)
Any Gr 2-5 CAR related Gr 3 Gr 4 Gr 5	4 (50.0%) 1 (12.5%) 2 (25.0%) 0 (0)	10 (66.7%) 2 (13.3%) 6 (40.0%) 0 (0)	5 (55.6) 2 (22.2%) 0 (0) 0 (0)	18 (60.0%) 5 (16.7%) 8 (26.7%) 0 (0)
Any Serious Gr 3 Gr 4 Gr 5	7 (87.5%) 2 (25.0%) 3 (37.5%) 1 (12.5%)	9 (60.0%) 1 (6.7%) 6 (40.0%) 1 (6.7%)	2 (22.2%) 0 (0) 1 (11.1%) 0 (0)	16 (53.3%) 3 (10.0%) 9 (30.0%) 2 (6.7%)

Derived from:
S:\CD19\Clinical Development\data\31AUG2014\derived\gen_inv_plan.sas
S:\CD19\Clinical Development\data\31AUG2014\TFLs from clinipace\IBTable2_G1.rtf
S:\CD19\Clinical Development\data\31AUG2014\TFLs from clinipace\IBTable2_G2.rtf
S:\CD19\Clinical Development\data\31AUG2014\TFLs from clinipace\IBTable2_G3.rtf
S:\CD19\Clinical Development\data\31AUG2014\TFLs from clinipace\IBTable3_G1.rtf
S:\CD19\Clinical Development\data\31AUG2014\TFLs from clinipace\IBTable3_G2.rtf
S:\CD19\Clinical Development\data\31AUG2014\TFLs from clinipace\IBTable3_G3.rtf
S:\CD19\Clinical Development\data\31AUG2014\TFLs from clinipace\TAE_6_13.rtf
S:\CD19\Clinical Development\data\31AUG2014\TFLs from clinipace\TAE_6_14.rtf
S:\CD19\Clinical Development\data\31AUG2014\TFLs from clinipace\TAE_6_15.rtf
S:\CD19\Clinical Development\data\31AUG2014\TFLs from clinipace\TAE_6_16.rtf

Adverse events that occurred in ≥ 10% of subjects are provided in Table 6. Specific adverse events that occurred in ≥ 20% of subjects includes lymphopenia 28 subjects (93.3%), neutropenia 27 subjects (90.0%), leukopenia 26 subjects (86.7%), febrile neutropenia (without documented infection) 21 subjects (70.0%), anemia 19 subjects (63.3%), thrombocytopenia 19 subjects (63.3%), hypotension 10 subjects (33.3%), infection (documented infection with neutropenia) 9 subjects (30%), pain (head/headache) 7 subjects (23.3%), hypophosphatemia 7 subjects (23.3%), creatinine 6 subjects (20.0%), fatigue 6 subjects (20.0%), and fever (without neutropenia) 6 subjects (20.0%).

Table 6. Adverse Events ≥ 10% of Subjects

CTC Term	Any Gr 2-5	≥ Grade 3	Grade 3	Grade 4	Grade 5
Subject incidence of adverse events - n (%) (N=30)					
Any Adverse Event	29 (96.7)	29 (96.7)	1 (3.3)	26 (86.7)	2 (6.7)
Lymphopenia	28 (93.3)	28 (93.3)	1 (3.3)	27 (90.0)	0 (0.0)
Neutropenia	27 (90.0)	27 (90.0)	6 (20.0)	21 (70.0)	0 (0.0)
Leukopenia	26 (86.7)	26 (86.7)	4 (13.3)	22 (73.3)	0 (0.0)
Febrile neutropenia (fever of unknown origin without clinically or microbiologically documented infection)(ANC <1.0 x 10e9/L, fever ≥38.5 degrees C)	21 (70.0)	21 (70.0)	21 (70.0)	0 (0.0)	0 (0.0)
Anemia	19 (63.3)	19 (63.3)	19 (63.3)	0 (0.0)	0 (0.0)
Thrombocytopenia	19 (63.3)	19 (63.3)	4 (13.3)	15 (50.0)	0 (0.0)
Hypotension	10 (33.3)	8 (26.7)	5 (16.7)	3 (10.0)	0 (0.0)
Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10e9/L)	9 (30.0)	9 (30.0)	9 (30.0)	0 (0.0)	0 (0.0)
Pain (Head/Headache)	7 (23.3)	7 (23.3)	7 (23.3)	0 (0.0)	0 (0.0)
Hypophosphatemia	7 (23.3)	7 (23.3)	7 (23.3)	0 (0.0)	0 (0.0)
Creatinine	6 (20.0)	6 (20.0)	4 (13.3)	2 (6.7)	0 (0.0)
Fatigue	6 (20.0)	6 (20.0)	6 (20.0)	0 (0.0)	0 (0.0)
Fever (without neutropenia)	6 (20.0)	2 (6.7)	2 (6.7)	0 (0.0)	0 (0.0)
Acute vascular leak syndrome	5 (16.7)	5 (16.7)	4 (13.3)	1 (3.3)	0 (0.0)
Hypocalcemia	5 (16.7)	5 (16.7)	5 (16.7)	0 (0.0)	0 (0.0)
Confusion	4 (13.3)	3 (10.0)	3 (10.0)	0 (0.0)	0 (0.0)
Dyspnea	4 (13.3)	3 (10.0)	3 (10.0)	0 (0.0)	0 (0.0)
Hypoxia	5 (16.7)	4 (13.3)	3 (10.0)	1 (3.3)	0 (0.0)
Infection with normal ANC	5 (16.7)	5 (16.7)	5 (16.7)	0 (0.0)	0 (0.0)
Hypoalbuminemia	4 (13.3)	4 (13.3)	4 (13.3)	0 (0.0)	0 (0.0)
Infection urinary tract NOS with normal ANC	4 (13.3)	3 (10.0)	3 (10.0)	0 (0.0)	0 (0.0)
Aphasia/Dysphasia	4 (13.3)	2 (6.7)	0 (0.0)	2 (6.7)	0 (0.0)
Transaminase elevation	3 (10.0)	3 (10.0)	3 (10.0)	0 (0.0)	0 (0.0)
Anxiety	3 (10.0)	1 (3.3)	0 (0.0)	1 (3.3)	0 (0.0)
Neuropathy: Motor	3 (10.0)	2 (6.7)	2 (6.7)	0 (0.0)	0 (0.0)
Hyponatremia	3 (10.0)	3 (10.0)	3 (10.0)	0 (0.0)	0 (0.0)
Thrombosis	3 (10.0)	3 (10.0)	1 (3.3)	1 (3.3)	1 (3.3)
Derived from: S:\CD19\Clinical Development\data\31AUG2014\TFLs from clinipace\IBTable2.rtf					

Adverse Events Attributed to anti-CD19 CAR+ T cells

Adverse events attributed to anti-CD19 CAR+ T cells by the investigator that occurred in ≥ 10% of subjects are provided in Table 7. These events include hypotension 5 subjects (16.7%), elevated creatinine 4 subjects (13.3%), speech impairment 4 subjects (13.3%), confusion 3 subjects (10.0%), fever 3 subjects (10.0%), and somnolence 3 subjects (10.0%).

Table 7. Adverse Events Attributed to anti-CD19 CAR+ T cells

CTC Term	Any Gr 2-5	≥ Grade 3	Grade 3	Grade 4	Grade 5
Subject incidence of adverse events - n (%) (N=30)					
Any Adverse Event	18 (60.0%)	13 (43.3%)	5 (16.7%)	8 (26.7%)	0 (0.0%)
Hypotension	5 (16.7%)	4 (13.3%)	1 (3.3%)	3 (10.0%)	0 (0.0%)
Creatinine	4 (13.3%)	3 (10.0%)	1 (3.3%)	2 (6.7%)	0 (0.0%)
Speech impairment (e.g., dysphasia or aphasia)	4 (13.3%)	2 (6.7%)	0 (0.0%)	2 (6.7%)	0 (0.0%)
Confusion	3 (10.0%)	2 (6.7%)	2 (6.7%)	0 (0.0%)	0 (0.0%)
Fever (in the absence of neutropenia, where neutropenia is defined as ANC <1.0 x 10e9/L)	3 (10.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Somnolence/depressed level of consciousness	3 (10.0%)	3 (10.0%)	0 (0.0%)	3 (10.0%)	0 (0.0%)
Derived from: *S:\CD19\Clinical Development\data\31AUG2014\TFLs from clinipace\TAE_6_9.rtf* *S:\CD19\Clinical Development\data\31AUG2014\TFLs from clinipace\IBTable3.rtf*					

Dose-Limiting Toxicity

Using the definition of DLT described in the NCI study, the incidence of DLT within Groups 1, 2 and 3 was 38%, 40%, and 0%, respectively (Data on File, Kite Pharma). With the exception of subject 1010002, DLTs were primarily neurotoxicities, 2 cases of elevated creatinine, and 1 event each of hypoxia and hypotension. Table 8 provides a listing of DLTs. In Group 3 there were no DLTs reported. The conditioning regimen in Group 3 is now being studied with 2 x 10^6 anti-CD19 CAR+ T cells/kg in the NCI Protocol 09-C-0082.

Table 8. Dose-Limiting Toxicities

Subject No.	Anti-CD19 CAR+ T cells/kg	Dose-Limiting Toxicities (DLT)	Group	Comment
1010002	3 X 10^6	G4 hypoxia G4 influenza infection G5 thrombosis (cerebral thrombi with global infarction)	1	The subject had a culture-proven H1N1 viral pneumonia and died 18 days after his infusion.
1010004	2.5 X 10^6	G4 creatinine	2	Required dialysis
1010007	28 X 10^6	G4 somnolence	1	Required intubation
1010008	30 X 10^6	G4 somnolence	1	Required intubation
1010009	5 X 10^6	G3 confusion/ aphasia G3 cranial nerve VII neuropathy	2	
1010010	4 X 10^6	G3 intermittent confusion/aphasia	2	
1010014	2.5 X 10^6	G3 hypoxia G4 hypotension G3 creatinine G4 somnolence/intermittent confusion	2	Required intubation
1010015	2.5 X 10^6	G4 myoclonus G4 expressive aphasia	2	Required intubation
1010021	1 X 10^6	G4 aphasia G3 motor neuropathy	2	

Group 1: high dose chemotherapy conditioning; IL-2
Group 2: high dose chemotherapy conditioning; no IL-2
Group 3: low dose chemotherapy conditioning; no IL-2

Derived from:
S:\CD19\Clinical Development\data\31AUG2014\TFLs from clinipace\ LAE_1_1.rtf
S:\CD19\Clinical Development\data\31AUG2014\derived\ subject 1010021 DLT NTF 19SEP2014.doc

Cytokine Release Syndrome

Cytokine release is induced by the activated T cells upon engagement with the CD19 target. Using a broad search strategy, treatment-emergent adverse events which may be attributed to CRS include fever, febrile neutropenia, hypotension, acute vascular leak syndrome, elevated creatinine, renal failure, hypoxia, and pleural effusion.

Table 9 provides the incidence of potential CRS adverse events. Twenty six (26) (86.7%) subjects reported adverse events which could be attributed to cytokine release, where 24 subjects (80.0%) reported a ≥ grade 3 event and 6 subjects (20.0%) experienced a serious event. Adverse events due to co-therapies such as IL-2 (used in Group 1) and conditioning chemotherapy (causing febrile neutropenia) potentially confound this analysis.

Clinical manifestations of CRS occurred typically in the first week after anti-CD19 CAR+ T cell infusion and were less common in the subjects in Group 3. Only 1 of the 9 subjects in Group 3 experienced grade 3 hypotension, and 4 experienced fever (3 subjects experienced grade 3 fever and 1 subject

experienced grade 2 fever). Events of acute vascular leak syndrome, oliguria, elevated creatinine, and renal failure were reported only in subjects in Groups 1 and 2 (data on file, Kite Pharma).

Table 9. Cytokine Release Syndrome Adverse Events

	Any Gr 2-5 (N = 30)	≥ Grade 3 (N = 30)	Grade 3 (N = 30)	Grade 4 (N = 30)	Grade 5 (N = 30)
Subject incidence of CRS events - n (%)	26 (86.7%)	24 (80.0%)	18 (60.0%)	6 (20.0%)	0 (0.0%)
Febrile neutropenia (fever of unknown origin without clinically or microbiologically documented infection)(ANC <1.0 x 10e9/L, fever >=38.5 degrees C)	21 (70.0%)	21 (70.0%)	21 (70.0%)	0 (0.0%)	0 (0.0%)
Hypotension	10 (33.3%)	8 (26.7%)	5 (16.7%)	3 (10.0%)	0 (0.0%)
Creatinine	6 (20.0%)	6 (20.0%)	4 (13.3%)	2 (6.7%)	0 (0.0%)
Fever (in the absence of neutropenia, where neutropenia is defined as ANC <1.0 x 10e9/L)	6 (20.0%)	2 (6.7%)	2 (6.7%)	0 (0.0%)	0 (0.0%)
Acute vascular leak syndrome	5 (16.7%)	5 (16.7%)	4 (13.3%)	1 (3.3%)	0 (0.0%)
Hypoxia	5 (16.7%)	4 (13.3%)	3 (10.0%)	1 (3.3%)	0 (0.0%)
Renal failure	2 (6.7%)	2 (6.7%)	2 (6.7%)	0 (0.0%)	0 (0.0%)
Pleural effusion (non-malignant)	1 (3.3%)	1 (3.3%)	1 (3.3%)	0 (0.0%)	0 (0.0%)
Subject incidence of serious CRS events	6 (20.0%)	6 (20.0%)	2 (6.7%)	4 (13.3%)	0 (0.0%)
Derived from: *S:\CD19\Clinical Development\data\31AUG2014\TFLs from clinipace\TAE_7_1.rtf* *S:\CD19\Clinical Development\data\31AUG2014\derived\ CRS_neuro_summary.doc*					

Neurologic Adverse Events

Table 10 provides all neurologic adverse events, predominantly confusion, aphasia/dysphasia, motor and somnolence. Twelve subjects (40%) had severe ≥ grade 3 neurotoxicity, and 11 subjects (36.7%) experienced a serious event.

The subject who died with a neurotoxicity had an event of CNS cerebrovascular ischemia in the context of viral influenza A infection. This was deemed unrelated to the anti-CD19 CAR+ T cells by the investigator.

Five subjects (16.7%) with neurotoxicity events required mechanical ventilation for airway protection for neurological adverse events; all of these subjects were in Groups 1 and 2. There has been no subjects intubated in Group 3.

Neurologic adverse events had a median onset of 6 days ranging between days 2 and 17 post anti-CD19 CAR+ T cell infusion, with the exception of grade 4 myelitis which occurred in 1 subject and had an onset at day 110 post anti-CD19 CAR+ T cell infusion. Given the time of onset, presentation and brain MRI findings, this event was considered by the investigator to be related to fludarabine and not attributed to the anti-CD19 CAR+ T cells. The median time to resolution of the neurological adverse event to grade 1 or better was 14 days post infusion.

Table 10. Neurologic Events

CTC Term	Any Gr 2-5 (N = 30)	≥ Grade 3 (N = 30)	Gr 3 (N = 30)	Gr 4 (N = 30)	Gr 5 (N = 30)
Subject incidence of neurologic events - n (%)	17 (56.7%)	12 (40.0%)	5 (16.7%)	7 (23.3%)	0 (0.0%)
Confusion	4 (13.3%)	3 (10.0%)	3 (10.0%)	0 (0.0%)	0 (0.0%)
Speech impairment (e.g., dysphasia or aphasia)	4 (13.3%)	2 (6.7%)	0 (0.0%)	2 (6.7%)	0 (0.0%)
Neuropathy: motor	3 (10.0%)	2 (6.7%)	2 (6.7%)	0 (0.0%)	0 (0.0%)
Somnolence/depressed level of consciousness	3 (10.0%)	3 (10.0%)	0 (0.0%)	3 (10.0%)	0 (0.0%)
Encephalopathy	2 (6.7%)	2 (6.7%)	1 (3.3%)	1 (3.3%)	0 (0.0%)
Ataxia (incoordination)	1 (3.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
CNS cerebrovascular ischemia	1 (3.3%)	1 (3.3%)	0 (0.0%)	1 (3.3%)	0 (0.0%)
Dizziness	1 (3.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Myelitis	1 (3.3%)	1 (3.3%)	0 (0.0%)	1 (3.3%)	0 (0.0%)
Neuropathy: cranial::CN III Pupil, upper eyelid, extra ocular movements	1 (3.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Neuropathy: cranial::CN VII Motor-face; Sensory-taste	1 (3.3%)	1 (3.3%)	1 (3.3%)	0 (0.0%)	0 (0.0%)
Neuropathy: sensory	1 (3.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Pyramidal tract dysfunction (e.g., increased tone, hyperreflexia, positive Babinski, decreased fine motor coordination	1 (3.3%)	1 (3.3%)	0 (0.0%)	1 (3.3%)	0 (0.0%)
Seizure	1 (3.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Tremor	1 (3.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Subject incidence of serious neurotoxicity events[a]	11 (36.7%)	9 (30.0%)	2 (6.7%)	7 (23.3%)	0 (0.0%)
Subject incidence of mechanical ventilation for the management of neurotoxicity[b]	5 (16.7%)	5 (16.7%)	0 (0.0%)	5 (16.7%)	0 (0.0%)
Median (range) onset day of neurotoxicity[c] (gr 2-5)	6 (2, 17)				
Median days to resolution to grade 1 or better (from the day of cell dose)	14 (9, 41)				

[a] Two serious events were reported with grade < 3; grade 2 seizure and grade 2 aphasia.

Derived from:
S:\CD19\Clinical Development\data\31AUG2014\TFLs from clinipace\TAE_7_1.rtf
S:\CD19\Clinical Development\data\31AUG2014\derived\ CRS_neuro_summary.doc
Data set aeaeae.xls.

Deaths

Two subjects died within 30 days of the anti CD19 CAR+ T cell infusion. Subject 2, as described above, died 18 days after investigational treatment due to a cerebral infarction concurrent with viral pneumonia, influenza A infection, E coli infection, dyspnea, and hypoxia. Subject 11 had PMBCL, with extensive fibrotic mediastinal lymphoma involvement, died 16 days after investigational treatment. No cause of death determined on autopsy and the autopsy report concluded likely cause of death was cardiac arrhythmia given the mediastinal involvement of PMBCL (Kochenderfer 2014). Neither event was deemed related to anti-CD19 CAR+ T cells by the investigator.

2.3.4 KTE-C19

Kite Pharma is developing an eACT™ (KTE-C19) that targets CD19 expression on B cell malignancies. The CAR vector construct is identical to the one used in NCI protocol 09-C-0082. Kite Pharma in conjunction with the NCI Surgery Branch has developed a rapid, closed, **and bead-less process for the generation of the anti-CD19 CAR+ T cells. Closing the process retains the characteristics of the T cell product (Better 2014). See the investigational product manual for more details.**

3 Study Design

3.1 General Study Design

Study KTE-C19-101 is a phase 1-2 multicenter, open-label study evaluating the safety and efficacy of KTE-C19 in subjects with refractory NHL. Study KTE-C19-101 will be separated into two distinct phases designated as phase 1 and phase 2.

During phase 1, approximately 6-12 subjects, with DLBCL, PMBCL or TFL will be enrolled to evaluate the safety of KTE-C19 at a target dose of 2 x 10^6 anti-CD19 CAR+ T cells/kg (± 20%; 1.6 x 10^6 anti-CD19 CAR+ T cells/kg to 2.4 x 10^6 anti-CD19 CAR+ T cells/kg). If the regimen is safe based on the incidence of DLT, phase 2 will open to enrollment. If the initial regimen is not safe, a lower dose of 1 x 10^6 anti-CD19 CAR+ T cells/kg may be evaluated in an additional 6-12 subjects. A safety review team (SRT), that is internal to the study sponsor and in collaboration with at least one study investigator, will review the safety data and make recommendations on further study conduct of phase 1 as outlined in Section 9.6.

In phase 2, subjects will enroll into 2 separate cohorts designated as cohort 1 and cohort 2.

- Cohort 1 will enroll adult subjects with refractory DLBCL
- Cohort 2 will enroll adult subjects with refractory PMBCL and TFL
    - TFL is defined as subjects who received prior chemotherapy for follicular lymphoma

Independent of the phase of the study (phase 1 or phase 2) or which cohort (cohort 1 or cohort 2 of phase 2 only) each subject will follow the same study treatment schedule and procedural requirements. Each subject will proceed through the following study periods:

- Screening/ Leukapheresis period
- Conditioning chemotherapy period
- Investigational Product (IP) treatment period
- Post treatment assessment period
- Long-term follow-up period

During phase 2 of the study, an independent Data Safety Monitoring Board (DSMB) will meet 2 times when 20 and 50 subjects enrolled into cohort 1 have completed their 3 month disease assessment. The

DSMB will review safety and efficacy data and be chartered to make trial conduct recommendations based on an analysis of risk vs. benefit. The DSMB may meet more often as needed.

For study requirements assigned to each study period, please refer to the schedule of assessments (SOA) and Section 7 for details.

A study schema is drawn out and described at the end of the protocol synopsis section.

3.2 Participating Sites

Approximately 25 centers located in North America will participate in this study. During the conduct of the study, additional regions, countries or sites may be added as necessary.

Sites that do not enroll a subject within 3 months of their site being activated, will be considered for closure.

3.3 Number of Subjects

Participants in this trial will be referred to as "subjects". It is anticipated that approximately 118-124 subjects will be enrolled into this study as defined below:

Phase 1: approximately 6-12 subjects

Phase 2: approximately 112 subjects enrolled into 2 cohorts

- Cohort 1: Approximately 72 subjects
- Cohort 2: Up to 40 subjects

It should be noted that Kite Pharma may choose to close enrollment at any time. Please refer to the statistical considerations section of the protocol for sample size estimations.

3.4 Replacement of Subjects

Subjects who withdraw from the study prior to the initiation of conditioning chemotherapy may be replaced.

3.5 Study Duration

3.5.1 Study Duration for Individual Subjects

For an individual subject, the length of participation includes up to 28 day screening period, a 5 day conditioning chemotherapy treatment period, a KTE-C19 treatment period (which includes a 7 day in-hospital recovery period), a post treatment assessment period and a long term follow-up period (survival surveillance for up to 15 years).

The duration of the study for individual subjects will vary. For a subject who completes the entire protocol from the date of informed consent through the completion of the long term follow-up period, the duration of the study will take approximately 15 years and 2 months to complete. However, individual study duration will vary depending on a subject's screening requirements, response to treatment and survival.

Subjects will be followed for all adverse events for 3 months after treatment. After that, the need for prolonged follow-up is based on the potential persistence of gene transfer vectors in treated subjects. After 3 months, subjects will be monitored for targeted adverse events/serious adverse events (e.g. hematological, neurological, second malignancies, infections or autoimmune disorders) and presence of

replication competent retrovirus (RCR) in subjects blood at intervals outlined in the schedule of assessments (SOA).

3.5.2 Completion of Study

Completion of the study is defined as the time at which the last subject completes the long term follow-up period visit, is considered lost to follow-up, withdraws consent, or dies. The primary analyses will be conducted when all subjects in cohort 1 and the overall study population respectively have completed the 6 month disease response assessment, are lost to follow-up, withdraw from the study, or die, whichever occurs first.

4 Subject Screening and Enrollment

All subjects or legally appointed representatives/caregivers, must personally sign and date the IRB/IEC approved consent form before initiating any study specific procedures or activities that are not part of subjects routine care, please refer to Section 7 for details.

Each subject who enters the screening period will receive a unique subject identification number before any study specific procedures or activities are initiated per the enrollment instruction manual. This number will be used to identify the subject throughout the study and must be used on all study documentation related to the subject.

Furthermore, the subject identification number must remain constant throughout the entire clinical study, it must not be changed after enrollment or if the subject is rescreened or retreated.

5 Subject Eligibility

5.1 Inclusion Criteria

101. Histologically confirmed aggressive B cell NHL, including the following types defined by WHO 2008:
    - DLBCL not otherwise specified; T cell/histiocyte rich large B cell lymphoma; DLBCL associated with chronic inflammation; Epstein-Barr virus (EBV)+ DLBCL of the elderly; Primary cutaneous DLBCL, leg type; OR
    - primary mediastinal (thymic) large B cell lymphoma
    - transformation of follicular lymphoma to DLBCL will also be included
102. Chemotherapy-refractory disease, defined as one or more of the following:
    - Stable disease **(duration of stable disease must be ≤ 12 months)** or progressive disease as best response to most recent chemotherapy containing regimen
    - Disease progression or recurrence ≤ 12 months of prior autologous SCT
103. Subjects must have received adequate prior therapy including at a minimum:
    - anti-CD20 monoclonal antibody unless investigator determines that tumor is CD20-negative **and**
    - an anthracycline containing chemotherapy regimen
    - **for** subjects with transformed FL must have received prior chemotherapy for follicular lymphoma and subsequently have chemorefractory disease after transformation to DLBCL
104. At least 1 measurable lesion according to the revised IWG Response Criteria for Malignant Lymphoma (Cheson 2007). Lesions that have been previously irradiated will be considered measurable only if progression has been documented following completion of radiation therapy
105. MRI of the brain showing no evidence of CNS lymphoma

106. Greater than or equal to 2 weeks must have elapsed since any prior radiation therapy or systemic therapy at the time the subject is planned for leukapheresis
107. Toxicities due to prior therapy must be stable or recovered to ≤ Grade 1 (except for clinically non-significant toxicities such as alopecia)
108. Age 18 or older
109. Eastern cooperative oncology group (ECOG) performance status of 0 or 1
110. ANC ≥ 1000/uL
111. Platelet count ≥ 50,000/uL
112. Adequate renal, hepatic, and cardiac function defined as:
    - Serum creatinine ≤ 1.5 mg/dL
    - Serum ALT/AST ≤ 2.5 ULN
    - Total bilirubin ≤ 1.5 mg/dl, except in subjects with Gilbert's syndrome.
    - Cardiac ejection fraction ≥ 50% and no evidence of pericardial effusion as determined by an ECHO.
113. Females of childbearing potential must have a negative serum or urine pregnancy test.

5.2 Exclusion Criteria

201. History of malignancy other than nonmelanoma skin cancer or carcinoma in situ (e.g. cervix, bladder, breast) or follicular lymphoma unless disease free for at least 3 years
202. History of Richter's transformation of CLL
203. Autologous stem cell transplant within 6 weeks of informed consent
204. History of allogeneic stem cell transplantation
205. Prior CD19 targeted therapy with the exception of subjects who received KTE-C19 in this study and are eligible for re-treatment
206. Prior chimeric antigen receptor therapy or other genetically modified T cell therapy
207. Clinically significant active infection (e.g. Simple UTI, bacterial pharyngitis allowed) or currently receiving IV antibiotics or have received IV antibiotics within 7 days prior to enrollment (Prophylaxis antibiotics, antivirals and antifungals are permitted)
208. **Known history of** infection with HIV or hepatitis B (HBsAg positive) or hepatitis C virus (anti-HCV positive)
209. Subjects with detectable cerebrospinal fluid malignant cells, or brain metastases, or with a history of cerebrospinal fluid malignant cells or brain metastases
210. History of a seizure disorder, cerebrovascular ischemia/hemorrhage, dementia, cerebellar disease, or any autoimmune disease with CNS involvement
211. Subjects with cardiac atrial or cardiac ventricular lymphoma involvement
212. Requirement for urgent therapy due to tumor mass effects such as bowel obstruction or blood vessel compression
213. Primary immunodeficiency
214. Any medical condition likely to interfere with assessment of safety or efficacy of study treatment
215. Current or expected need for systemic corticosteroid therapy. Note: Topical and inhaled corticosteroids in standard doses and physiologic replacement for subjects with adrenal insufficiency are allowed. Doses of corticosteroids of greater than or equal to 5 mg/day of prednisone or equivalent doses of other corticosteroids are not allowed.
216. History of severe immediate hypersensitivity reaction to any of the agents used in this study
217. Live vaccine ≤ 6 weeks prior to start of conditioning regimen
218. Women of child-bearing potential who are pregnant or breastfeeding because of the potentially dangerous effects of the preparative chemotherapy on the fetus or infant. Females

who have undergone surgical sterilization or who have been postmenopausal for at least 2 years are not considered to be of childbearing potential

219. Subjects of both genders who are not willing to practice birth control from the time of consent through 6 months after the completion of KTE-C19.
220. In the investigators judgment, the subject is unlikely to complete all protocol-required study visits or procedures, including follow-up visits, or comply with the study requirements for participation.

6 Protocol Treatment

6.1 Treatment Terminology

The investigational product for this study is named KTE-C19. The conditioning chemotherapy regimen for this study will be fludarabine and cyclophosphamide. The term study treatment refers to all protocol required therapies.

6.2 Study Treatment

6.2.1 KTE-C19

This section contains general information and is not intended to provide specific instructions. Refer to the investigational product manual for details and instruction on storage and administration.

KTE-C19 will be administered as a single infusion at a target dose of 2 x 10^6 anti-CD19 CAR+ T cells/kg (± 20%). **A minimum dose of 1 x 10^6 anti-CD19 CAR+ T cells/kg may be administered. For subjects weighing greater than 100 kg, a maximum flat dose of 2 x 10^8 anti-CD19 CAR+ T cells will be administered.**

KTE-C19 is supplied cryopreserved in cryostorage bags. The product in the bag is slightly cloudy, with cream to yellow color. The cryostorage bags containing KTE-C19 arrive frozen in a liquid nitrogen dry shipper. The bags must be stored in vapor phase of liquid nitrogen and the product remains frozen until the subject is ready for treatment to assure viable live autologous cells are administered to the subject. Several inactive ingredients are added to the product to assure viability and stability of the live cells through the freezing, thawing and infusion process.

Each bag contains a subject specific product, and the intended subject will be identified by subject ID number. The product should be thawed and administered to the subject as specified in the investigational product manual. The product must not be thawed until the subject is ready for the infusion.

To date, subjects have received doses of anti-CD19 CAR+ T cells ranging from 1-30 x 10^6 anti-CD19 CAR+ T cells/kg. There have been no instances of accidental overdose of subjects in this program. In case of accidental overdose, treatment should be supportive. Corticosteroid therapy may be considered if any dose is associated with severe toxicity.

If any problems related to the use of KTE-C19 or any products that support the management of KTE-C19 (e.g. cryostorage bags, subject identification labels) required in this study are identified, please log on to kitepharma.com and complete the user complaint form.

6.2.2 Conditioning Chemotherapy

Conditioning chemotherapy will be supplied by the investigative site unless otherwise noted. Sites should refer to the current product label for guidance on packaging, storage, preparation, administration and toxicity management associated with the administration of both agents.

Subjects will receive a non-myeloablative conditioning regimen consisting of fludarabine 30 mg/m^2/day and cyclophosphamide 300 mg/m^2/day, administered x 3 days in order to induce lymphocyte depletion and create an optimal environment for expansion of KTE-C19 in vivo.

6.2.2.1 Fludarabine

Fludarabine phosphate is a synthetic purine nucleoside that differs from physiologic nucleosides in that the sugar moiety is arabinose instead of ribose or deoxyribose. Fludarabine is a purine antagonist antimetabolite.

Refer to the most recent version of the package insert for specific details surrounding the administration of fludarabine.

6.2.2.2 Cyclophosphamide

Cyclophosphamide is a nitrogen mustard-derivative alkylating agent. Following conversion to active metabolites in the liver, cyclophosphamide functions as an alkylating agent; the drug also possesses potent immunosuppressive activity. The serum half-life after IV administration ranges from 3-12 hours; the drug and/or its metabolites can be detected in the serum for up to 72 hours after administration.

Refer to the most recent version of the package insert for specific details surrounding the administration of cyclophosphamide.

6.2.3 Concomitant Therapy

During the course of the study, investigators may prescribe any concomitant medications or treatment deemed necessary to provide adequate supportive care except those medications listed in the excluded medication Section 6.2.4

All concurrent therapies, including medications, intubation, dialysis, and blood products, should be recorded from the date of the consent through 3 months after completing treatment with KTE-C19. After 3 months of follow-up, targeted concomitant medication will be collected including gammaglobulin, immunosuppressive drugs, anti-infective drugs, vaccinations, and any therapy for the treatment of the subject's disease for two years beyond disease progression.

Specific concomitant medication collection requirements and instructions are included in the case report form (CRF) completion guidelines.

6.2.4 Excluded Medications

Corticosteroid therapy at a pharmacologic dose (≥ 5 mg/day of prednisone or equivalent doses of other corticosteroids) and other immunosuppressive drugs should be avoided until 3 months after KTE-C19 administration, unless medically indicated to treat new toxicity.

Medications that might interfere with the evaluation of the investigational product should not be used unless absolutely necessary. Medications in this category include, but are not limited to: immunosuppressants and corticosteroidal/non-steroidal anti-inflammatory agents including prednisone, dexamethasone, solumedrol, cyclosporine and ibuprofen. If permissibility of a specific medication/treatment is in question, please contact the Kite Pharma medical monitor on the title page.

Treatment for the subject's lymphoma such as chemotherapy, immunotherapy, targeted agents, radiation, and high dose corticosteroid, other than defined/allowed in this protocol, and other investigational agents are prohibited except as needed for treatment of disease progression.

6.2.5 Subsequent Therapy

Subsequent therapy for a subjects' disease such as non-study specified chemotherapy, immunotherapy, targeted agents, as well as stem cell transplant and radiation therapy must be collected in the CRFs as per the CRF completion guidelines.

6.3 Study Treatment Schedule

Subjects will undergo leukapheresis to obtain leukocytes (white blood cells) for the manufacturing of KTE-C19. Leukapheresed cells obtained at participating centers will be shipped to the Cell Processing Facility (CPF) over night as described in the investigational product manual.

Upon arrival at the CPF, each subject's leukapheresed product will be processed to enrich for the T cells containing PBMC fraction. T cells are then stimulated to expand and transduced with a retroviral vector to introduce the CAR gene. The T cells are then expanded and cryopreserved to generate the investigational product per CPF SOPs. Once the product has passed certain release tests, it will be shipped back to the treating facility. Following completion of each subjects' conditioning chemotherapy regimen, subjects will receive their respective KTE-C19 infusion.

6.3.1 Leukapheresis (Within approximately 5 days of enrollment)

Mononuclear cells will be obtained by leukapheresis **(12-15 liter apheresis with a goal to target approximately 5-10 x 10^9 mononuclear cells).** The leukapheresed cells are then packaged for expedited shipment to the CPF as described in the investigational product manual.

6.3.2 Fludarabine and Cyclophosphamide (Days -5 through -3 before infusion of KTE-C19)

The 3 day conditioning regimen of fludarabine and cyclophosphamide will be administered in accordance with the below daily dosing instructions.

- The IV hydration is 1L of 0.9% NaCl given prior to cyclophosphamide **on the day of infusion** followed by:
- Fludarabine 30mg/m^2 IV over 30 minutes followed by:
- Cyclophosphamide 300mg/m^2 IV over 60 minutes followed by:
- An additional 1L of 0.9% NaCl **at the completion of the cyclophosphamide infusion**

Subjects should be instructed to drink plenty of liquids during and for 24 hours following the chemotherapy (approximately 2 liters/24 hours). In general subjects should be kept well-hydrated but closely monitored to prevent fluid overload.

6.3.3 KTE-C19 (Day 0, 2 days after the last dose of Fludarabine and Cyclophosphamide):

Subjects will be hospitalized to receive treatment with KTE-C19 followed by a recovery period. Subjects will remain in the hospital through day 7 post treatment with KTE-C19. Subjects should not be discharged from the hospital until all KTE-C19-related non-hematological toxicities return to grade 1 or less. Subjects may be discharged with non-critical and clinically stable or slowly improving toxicities (eg renal insufficiency) even if > grade 1, if deemed appropriate by the investigator. Subjects should remain hospitalized for ongoing anti-CD19 CAR+ T cell-related fever, hypotension, hypoxia, or ongoing neurological toxicity greater than grade 1, or if deemed necessary by the treating investigator.

KTE-C19 is a subject-specific product. Upon receipt, verification that the product and subject-specific labels match the specific subject information is essential. Do not infuse the product if the information on the subject-specific label does not match the intended subject.

- The product will be checked by 2 personnel in accordance with institutional practice for the administration of cell products.
- KTE-C19 are to be thawed as described in the investigational product manual in accordance with institutional policy
- Upon thawing of the KTE-C19 T cells, KTE-C19 must be administered according to the investigational product manual.
- KTE-C19 at a target dose of 2 x 10^6 anti-CD19 CAR+ T cells/kg (± 20%) is to be infused intravenously over a time period not to exceed 30 minutes via non-filtered tubing; the bag should be gently agitated during infusion to prevent cell clumping.
- Subjects must remain hospitalized through day 7 following KTE-C19 administration at a minimum, to ensure monitoring and documentation of potential toxicities related to the cell product.
- The volume of T cells infused, the thaw time, the start time, and the stop time will all be noted in the subject medical record.

6.4 Toxicity Management

6.4.1 Infection Prophylaxis

Subjects should receive prophylaxis for infection with pneumocystis pneumonia, herpes virus, and fungal infections according to NCCN guidelines or standard institutional practice.

6.4.2 Tumor Lysis Syndrome

All subjects with significant malignancy burden and without a contradiction such as allergy should be started on prophylaxis (e.g. allopurinol) as per institutional guidelines prior to KTE-C19 infusion. Prophylaxis should be discontinued when the risk of tumor lysis has passed.

6.4.3 B Cell Depletion

It is possible that B cell depletion and hypogammaglobulinemia will occur due to the effects of KTE-C19 on normal B cells. Gammaglobulin will be administered for hypogammaglobulinemia according to institutional guidelines. At a minimum, trough IgG levels should be kept above 400 mg/dL, especially in the setting of infection (i.e. Center for International Bone Marrow Transplant Research, American Society for Bone and Morrow Transplantation).

6.4.4 Cytokine Release Syndrome

Cytokine release syndrome (CRS) is a symptom complex associated with the use of monoclonal antibodies and adoptive cell therapies that activate lymphocytes. The condition results from the release of cytokines from cells targeted by antibodies, immune effector cells recruited to the tumor area and subject's immune cells activated during this process. When cytokines are released, a variety of clinical signs and symptoms associated with CRS present themselves including cardiac, gastrointestinal, laboratory (coagulation, renal and hepatic), neurological, respiratory, skin, vascular (hypotension) and constitutional (fever, rigors, headaches malaise, fatigue arthralgia, nausea and vomiting).

The goal of CRS management in anti-CD19 CAR+ T cell therapy is to prevent life-threatening conditions while preserving the benefits of antitumor effects. In grading CRS, a CRS severity scale associated with antibody therapeutics was published by NCI investigators. Appreciating the scale needed to be adapted

for other therapeutics, to define mild, moderate, severe and life-threatening events, account for overlapping symptoms and guide treatment recommendations, a CRS revised grading system was created by Lee et al. and is highlighted below (Lee 2014). This grading scale outlined in Table 11, and subsequent treatment guidance outlined in Table 12, will be used for study KTE-C19-101.

Table 11. CRS Grading Scale

Grade 1	Symptoms are not life threatening and require symptomatic treatment only (e.g. fever, nausea, fatigue, headache, myalgia, malaise)
Grade 2	Symptoms require and respond to moderate intervention Oxygen requirement <40% or hypotension responsive to fluids or low dose of one vasopressor or Grade 2 organ toxicity
Grade 3	Symptoms require and respond to aggressive intervention Oxygen requirement ≥ 40% or hypotension requiring high dose or multiple vasopressors or Grade 3 organ toxicity or Grade 4 transaminitis
Grade 4	Life-threatening symptoms Requirements for ventilator support or Grade 4 organ toxicity (excluding transaminitis)
Grade 5	Death

The following algorithm outlined in Table 12 uses the CRS grading system outlined in Table 11 and is recommended to direct the management of CRS associated with treatment with KTE-C19. This CRS management strategy is based on the experience to date with anti-CD19 CAR+ T cell products (Lee 2014).

Table 12. Modified CRS Treatment Guidance

Cytokine Release Syndrome Grading assessment	Extensive co-morbidities or older age? No/Yes	Treatment
Grade 1: • Fever (defined as ≥ 38.3°C) • Constitutional symptoms	N/A	• Vigilant supportive care • Assess for infection • Treat fever and neutropenia if present, monitor fluid balance, antipyretics, analgesics as needed
Grade 2: • Hypotension: responds to fluids or one low dose vasopressor • Hypoxia: responds to <40% O^2 • Organ toxicity: grade 2	No	• As above for grade 1 • Monitor cardiac and other organ function closely
Grade 2: • Hypotension: responds to fluids or one low dose vasopressor • Hypoxia: responds to <40% O^2 • Organ toxicity: grade 2	Yes	• As above for grade 2 • Consider tocilizumab ± corticosteroids
Grade 3: • Hypotension: requires multiple vasopressors or high dose vasopressors • Hypoxia: requires ≥ 40% O^2 • Organ toxicity: grade 3, grade 4, transaminitis	N/A	
Grade 4 • Mechanical ventilation • Organ toxicity: grade 4 excluding transaminitis	N/A	

There have been reports that some of the severe cytokine release symptoms respond rapidly to infusion of tocilizumab, a monoclonal antibody to the IL-6 receptor in subjects treated with other anti-CD19 CAR+ T cell products (Davila 2014). Tocilizumab can be considered as per the table above or under the below circumstances if the listed disorders are thought to be due to cytokine release.

- Left ventricular ejection fraction 40% or less by echocardiogram
- Creatinine greater than 3-fold higher than the most recent level prior to anti-CD19 CAR+ T cell infusion
- Norepinephrine requirement for 36 hours since the first administration of norepinephrine even if norepinephrine administration was not continuous.

Tocilizumab is administered at a dose of 4 - 8 mg/kg infused IV over 1 hour (dose should not exceed 800 mg).

If no improvement in symptoms occur after tocilizumab infusion, consider other agents such as methylprednisolone 1 mg/kg every 12 hours.

6.4.4.1 Fever and Neutropenia

Evaluation for a source of infection should be performed per institutional guidelines. Fevers should be treated with acetaminophen and comfort measures. NSAIDs and corticosteroids should be avoided. Subjects who are neutropenic and febrile should receive broad-spectrum antibiotics. Maintenance IV fluids (normal saline) should be started on most subjects with high fevers, especially if oral intake is poor or if the subject has tachycardia. Strive for an even daily fluid balance in subjects who are not hypotensive and not experiencing active tumor lysis syndrome.

Filgrastim should be used according to published guidelines (e.g. Infectious Disease Society of America).

6.4.4.2 Blood Product Support

All blood products should be irradiated. Using CBC's as a guide, the subject should receive platelets and packed red blood cells as needed. Attempts should be made to keep hemoglobin >8.0 gm/dL and platelets >20,000/mm^3. Leukocyte filters should be utilized for all blood and platelet transfusions to decrease sensitization to transfused WBC's and decrease the risk of CMV infection.

6.4.4.3 Neurotoxicity

Neurotoxicity (e.g. encephalopathy, somnolence, aphasia) have been observed with anti-CD19 CAR+ T cell therapies. **Evaluation of any new onset neurotoxicity should include a neurological examination (including a MMSE), brain MRI, and examination of the cerebrospinal fluid (CSF) as clinically indicated. Endotracheal intubation may be needed for airway protection in severe cases. Corticosteroids may be considered for any severe or life-threatening neurotoxcity and anti-seizure and sedatives may be considered as clinically indicated.**

6.4.4.4 Hypotension and Renal insufficiency

Hypotension and renal insufficiency should be treated as described here or according to medical judgment and institutional practice guidelines. In general subjects should be kept well-hydrated but closely monitored to prevent fluid overload. The below management suggestions may need to be modified based on the clinical characteristics of individual subjects such as pulmonary status, cardiac function, and other factors.

The baseline systolic blood pressure is defined for this guideline as the average of all systolic blood pressure readings obtained during the 24 hours prior to the KTE-C19 infusion. The first treatment for hypotension is administration of IV normal saline boluses.

- Subjects with a systolic blood pressure that is 80% or less of their baseline blood pressure and less than 100 mm Hg should receive a 1 L normal saline bolus.
- Subjects with a systolic blood pressure that is 80% or less of their baseline blood pressure and greater than 100 mm Hg on two consecutive blood pressure checks separated by at least 2 hours should receive a 1 L normal saline bolus.
- Subjects with a systolic blood pressure less than 85 mm Hg should receive a 1 L normal saline bolus regardless of baseline blood pressure.

Please refer to Section 6.4.4 for the management of CRS.

7 Study Procedures

Research staff should refer to the SOAs for an outline of the procedures required. The visit schedule is calculated from KTE-C19 infusion on Day 0.

An overview of study assessments/procedures is outlined below. A description for each period of the study is provided in Section 7.11. Refer to the CRF completion guidelines for data collection requirements and documentation of study procedures.

7.1. Informed Consent

Before a subject's participation in the clinical study, the investigator is responsible for obtaining written informed consent from the subject or legally acceptable representative after adequate explanation of the study design, anticipated benefits and the potential risks. Subjects should sign the most current IRB/IEC approved ICF prior to any study specific activity or procedure is performed.

The consent process and the subject's agreement or refusal to participate in the study is to be documented in the subject's medical records. If the subject agrees to participate, the ICF is to be signed and personally dated by the subject (or legally acceptable representative) and by the person who conducted the informed consent discussion. The original signed ICF will be retained in accordance with institution policy and IRB/IEC requirements with a copy of the ICF provided to the subject (or legally acceptable representative).

All subjects who are enrolled into the study should be re-consented with any updated version of the IRB/IEC approved ICF if relevant to their participation in the study.

7.2 Demographic Data

Demographic data will be collected to include sex, date of birth, race, and ethnicity to study their possible association with subject safety and treatment effectiveness.

7.3 Medical and Treatment History

Relevant medical history prior to the start of adverse event reporting will be collected. Relevant medical history is defined as data on the subject's concurrent medical condition that would be typically shared in a referral letter. All findings will be recorded in the CRFs.

In addition to the medical history, all history related to the subject's disease, treatment and response to treatment will be collected and must date back to the original diagnosis.

For subjects who are being referred from another clinic or institution to the participating research center, copies from the subjects chart should be obtained.

7.4 Physical Exam, Vital Signs and Performance Status

Physical exams will be performed during screening and at times noted in the SOA. Changes noted in subsequent exams when compared to the baseline exam will be reported as an adverse event.

During IP administration/hospitalization, vital signs will be monitored before and after the KTE-C19 infusion and then routinely (every 4-6 hours) while hospitalized. If the subject has a fever (temperature 38.3^{o}C or greater) at any time during hospitalization, vital signs will be monitored more frequently as clinically indicated.

Performance status as measured by the ECOG scale and will be performed to quantify the subject's general well-being and ability to perform activities of daily life.

7.5 Neurocognitive Assessment

Neurocognitive assessments will be standardized by using the Mini Mental State Examination (MMSE) **standard version 2.0**. The MMSE is a 5-10 minute, 11-question measure that examines various areas of cognitive function: orientation, attention, immediate recall, short-term recall, language, and the ability to follow simple verbal and written commands.

The mini-mental state examination is divided into two sections. The first part requires vocal responses to the examiner's questions. In the second part of the exam, the subject is asked to follow verbal and written instructions, write a sentence spontaneously, and copy a geometric figure.

A full neurological assessment will be completed during screening to establish a baseline. Subsequent assessments will be performed before KTE-C19 administration on Day 0 and on day 1, 3, 5 and 7 as well as week 4 and month 3. Every attempt should be made to dedicate a single research staff member familiar with or trained in the administration of the MMSE to conduct the assessment to minimize inter-rater variability. If CNS symptoms persist, continue to perform the MMSE every two days until resolution of symptoms or discharged from the hospital.

7.6 Cardiac Function

Each subject's cardiac function as measured by Left Ventricular Ejection Fraction (LVEF) will be assessed during the screening period to confirm study eligibility. No evidence of pericardial effusion as required by eligibility will also be confirmed. Both LVEF and pericardial effusion will be assessed prior to study entrance by ECHO.

To establish a baseline, a 12-lead ECG will also be performed prior to initiating study treatment.

7.7 Magnetic Resonance Imaging

Each subject will undergo a screening Brain MRI to rule out CNS metastasis during the screening period of the study.

7.8 Laboratory

The following labs will be drawn at the time points indicated in the SOA.

- Sodium (Na), Potassium (K), Chloride (Cl), Total CO2 (bicarbonate), Creatinine, Glucose, Urea nitrogen (BUN), Albumin, Calcium total, Magnesium total (Mg), Inorganic Phosphorus, Alkaline Phosphatase, ALT/GPT, AST/GOT, Total Bilirubin, Direct Bilirubin, LD, Uric Acid (local lab)
- Complete Blood Count with Differential (local lab)
- Urinalysis (local lab)
- A urine or serum sample will be collected and assessed locally for females of childbearing potential. If the screening pregnancy test is positive, the subjects should not be enrolled. If a standard of care pregnancy test is collected during the course of the study, and the result is positive, the investigator should contact the Kite Pharma medical monitor for instructions. If a female partner of a male subject becomes pregnant during the conduct of the study, it must be reported by contacting Kite Pharma medical monitor for instructions.
- Blood draws for lymphocyte subsets, cytokine levels, RCR and CAR T+ cell for analysis at central lab
- Serum samples will also be evaluated for anti-KTE-C19 antibodies or human anti-mouse or anti-bovine antibodies, for analysis at central lab
    - **For serum samples that demonstrate increased anti-KTE-C19 human anti-mouse (HAMA) or anti-bovine (HABA) antibodies at the month 3 visit over baseline values, attempts**

should be made to obtain and test additional serum samples approximately every 3 months until the antibody levels return to baseline (or becomes negative) or up to 1 year from the completion of treatment, whichever occurs first.

7.9 Biomarkers

Biomarker analysis will be performed on blood and tumor samples to evaluate predictive and pharmacodynamic markers for KTE-C19. Prognostic markers in aggressive NHL may also be evaluated.

The presence, expansion, persistence, and immunophenotype of transduced anti-CD19 CAR+ T cells will be monitored in the blood primarily by PCR analysis, complemented by flow cytometry.

Levels of serum cytokines will also be evaluated in the blood. The following cytokines may be included in the panel: pro-inflammatory and immune modulating cytokines IL-6, TNFα, IL-8, IL-1, IL-2, GM-CSF, IL-15, IL-17a, IFNγ, IL-12p40/p70; immune effector molecules Granzyme A, B, Perforin, sFasL; correlates of acute phase response CRP, SAA and Chemokines MIP-1α, MIP-3α, IP-10, Eotaxin, MCP-4.

As KTE-C19 comprises retroviral vector transduced T cells, we will monitor the presence of replication-competent-retrovirus (RCR) in the blood of treated patients.

In addition, baseline leukapheresis and final KTE-C19 samples will be banked and may be analyzed by immunophenotyping and/or gene expression profiling. Remaining samples may be stored for future exploratory analysis of DNA, RNA, or protein markers.

Archived tumor tissue will be collected for central path review. Additional analysis may include CD19 expression, gene expression profiling, and analysis of DNA alterations. Remaining tumor samples may be stored for future exploratory analysis of DNA, RNA, or protein markers.

For subjects who sign the optional portion of the consent form (and for all subjects with accessible tumor at select sites), on-study paired core biopsies of tumor will be performed, at baseline and during the first month after treatment when we expect expansion and tumor infiltration with CAR T cells. In addition, persisting, relapsing or emerging lesions could also be biopsied to help determine eligibility for re-treatment or mechanisms of tumor resistance. Exploratory analysis of tumor or immune cell markers that correlate with response to KTE-C19 or disease prognosis will be analyzed.

These samples and any other components from these samples may be stored up to 15 years to address exploratory research scientific questions related to the treatment or disease under study. Each subject will have the right to have the sample material destroyed at any time by contacting the investigator who in turn can contact the central laboratory. The investigator should provide the sponsor the study and subject number so that the sample can be located and destroyed.

For subjects who withdraw consent, any samples that were not requested to be returned or destroyed will remain with the sponsor and any data that may be generated will be entered in the study database.

7.10 Disease Response Assessment

Subjects will be evaluated for disease response by the site investigator at times indicated in the SOA. Disease assessments will be evaluated per the revised IWG Response Criteria for Malignant Lymphoma (Cheson 2007). Flow cytometric, molecular or cytogenetic studies will not be used to determine response.

Baseline PET-CT scans of the neck, chest, abdomen and pelvis, along with the appropriate imaging of all other sites of disease are required. Subjects will have their first post KTE-C19 infusion planned PET-CT

tumor assessment 4 weeks following the KTE-C19 infusion and at regular intervals as highlighted in the SOA during the post treatment and long term follow-up portion of the study.

Post KTE-C19 administration disease assessments will be used to determine the time when progressive disease occurs. Subjects with symptoms suggestive of disease progression should be evaluated for progression at the time symptoms occur even if it is off schedule as per the SOA.

A bone marrow aspirate and biopsy will be performed in subjects who are being assessed for CR. Per the revised IWG Response Criteria for Malignant Lymphoma (Cheson 2007), a bone marrow aspirate and biopsy should be performed only when the subject had bone marrow involvement with lymphoma prior to therapy or if new abnormalities in the peripheral blood counts or blood smear cause clinical suspicion of bone marrow involvement with lymphoma after treatment. The bone marrow aspirate and biopsy must show no evidence of disease by morphology, or if indeterminate by morphology, it must be negative by immunohistochemistry to assign a CR to treatment.

In addition to the investigators assessment, PET-CT scans of all subjects evaluated for disease response for phase 2 will be submitted to and reviewed by an independent central reviewer. For subjects who discontinue the study due to an assessment of progressive disease which was not subsequently confirmed by a central radiology reviewer, any additional imaging data, subsequent to the image in question will be submitted to the central reviewer to confirm disease response.

If the subject is eligible for retreatment with KTE-C19, the last scan prior to retreatment will be considered the baseline for the purpose of evaluating the response to retreatment.

Requirements for PET-CT scans and shipping requirements will be outlined in the study imaging manual.

7.11 Description of Study Periods

Investigative sites will maintain a log of all screened subjects who were reviewed and evaluated for study participation. Information collected on the screening log should include limited information such as the date of screening, date the subject was enrolled or the reason for why the subject failed screening.

7.11.1 Screening

The screening period begins on the date the subject (or legally acceptable representative) signs the IRB/IEC approved ICF and continues through confirmation of eligibility and enrollment into the study. Informed consent must be obtained before completion of any study specific procedures. Procedures that are part of standard of care are not considered study specific procedures and may be performed prior to obtaining consent and used to confirm eligibility. Confirmation of this data must occur within the time allowance as outlined below and in the SOA.

After written informed consent has been obtained, subjects will be screened to confirm study eligibility and participation. Only subjects who meet the eligibility criteria listed in Section 5 will be enrolled into the study. If at any time the subject fails to meet the eligibility criteria the subject should be designated as a screen failure on the subject screening log with the reasons for failing screening.

The following assessments/procedures are to be completed during the screening period at the time points outlined in the SOA:

- Medical history and disease assessment
- Physical examination including weight and vital signs

- Subjects with symptoms of central nervous system malignancy such as new onset severe headaches, neck stiffness, or any focal neurologic findings on physical exam will have lumbar puncture for examination of cerebral spinal fluid.

- ECOG performance status
- Neurological assessment with MMSE
- ECG
- LVEF assessment (Note: may be performed within 8 weeks of treatment. To reduce subject burden an ECHO will be used for evaluation of LVEF and pericardial effusion).
- Imaging Studies
  - Brain MRI
  - Baseline PET CT of the neck, chest, abdomen and pelvis (if PET CT will be > 28 days at the initiation of conditioning chemotherapy, the scans must be repeated to establish a new baseline. PET CT should be taken as close to enrollment as possible).
- Labs
  - Chemistry panel
  - CBC with differential
  - Urine sample for urinalysis
  - β-HCG pregnancy test (serum or urine) on all women of child-bearing potential
- Adverse/Serious Adverse Event reporting (refer to Section 9 for safety reporting guidelines)
- Concomitant medications documentation and previous cancer treatment history
- Once eligibility confirmed, collection of archived tumor sample slides and fresh tumor sample(s) for subjects who signed the optional portion of the consent.

7.11.2 Rescreening

Subjects who fail to meet the eligibility criteria will be allowed to rescreen one time. Subjects will perform the assessment that initially resulted in the subject failing screening including any other procedures that fell outside of the designated screening window (i.e. lab assessments or PET-CT scans).

7.11.3 Leukapheresis

The following procedures/requirements will occur on the leukapheresis collection day and as outlined in the SOA:

- Leukapheresis
- Vital signs
- Weight
- Labs (to be drawn prior to leukapheresis)
  - Chemistry panel
  - CBC with differential
  - Anti-KTE-C19 antibodies
- Adverse/Serious Adverse Event reporting
- Concomitant medications documentation

7.11.4 Conditioning Chemotherapy Period

The following procedures will be completed during Day -5 to Day -1 at the time points outlined in the schedule of assessments:

- Fludarabine and cyclophosphamide administration
- Vital signs

- Labs (to be drawn prior to chemotherapy)
  - Chemistry Panel
  - CBC with differential
  - Lymphocyte subsets
  - Cytokine levels
- Adverse/Serious Adverse Event reporting
- Concomitant medications documentation

7.11.5 Investigational Product Treatment Period

Subjects will be hospitalized to receive treatment with KTE-C19 followed by a recovery period. **Subjects must have no evidence of clinically significant active infection, no clinically significant cardiac dysfunction, serum creatinine < 2.0 mg/dL, and no acute neurological toxicity > grade 1. Should an event exceed these criteria immediately prior to receiving KTE-C19, the KTE-C19 infusion must be held until the event resolves to the criteria above. If the KTE-C19 infusion is delayed > 2 weeks, conditioning chemotherapy must be repeated. In all cases of KTE-C19 infusion delays, contact the Kite medical monitor for guidance.**

Subjects will remain in the hospital through day 7 post treatment with KTE-C19. **Subjects should not be discharged from the hospital until all KTE-C19-related non-hematological toxicities return to grade 1 or less. Subjects may be discharged with non-critical and clinically stable or slowly improving toxicities (eg renal insufficiency) even if > grade 1 if deemed appropriate by the investigator. Subjects should remain hospitalized for ongoing anti-CD19 CAR+ T cell-related fever, hypotension, hypoxia, or ongoing neurological toxicity greater than grade 1, or if deemed necessary by the treating investigator.**

During this period, the following procedures will be completed at the time points outlined in the SOA:

- Mini mental status exam (MMSE)
  - MMSE will be administered before treatment with KTE-C19 on Day 0, then on every other day beginning with day 1 day 3, day 5 and day 7
- Vital signs Q4-6 hours during hospitalization
- Labs (before KTE-C19 infusion, as described in the SOA)
  - Chemistry Panel
  - CBC with differential
  - Lymphocyte subsets
  - Cytokine levels
  - Anti-CD19 CAR+ T cells
  - RCR analysis
- Infusion of KTE-C19
- Adverse/Serious Adverse Event reporting (refer to Section 9 for safety reporting guidelines)
- Concomitant medications documentation

7.11.6 Post Treatment Assessment Period

After completing KTE-C19 infusion and discharged from the hospital (typically on Day 8), all subjects will be followed in the post treatment assessment period. Counting from day 0 (KTE-C19 infusion), subjects will return to the clinic at the following intervals.

- Week 2
- Week 4 **(± 3 days)**
- Month 2 (± 1 week)
- Month 3 (± 1 week)

Subject will allow key sponsor contacts to continue to access medical records so that information related to subjects health condition and initial treatment response may be obtained. The following procedure will be completed for subjects as outlined in the SOA:

- MMSE
- PET-CT for disease assessment: If the PET-CT is not of high enough resolution, the scan must be repeated. Refer to the imaging charter for detailed instructions.
- Physical exam and vital signs
- Labs
  - Chemistry Panel
  - CBC with differential
  - β-HCG pregnancy test (serum or urine) on all women of child-bearing potential
  - Anti-KTE-C19 antibodies
  - Lymphocyte subsets
  - Cytokine levels
  - Anti-CD19 CAR+ T cells
  - RCR analysis
- Adverse/Serious Adverse Event reporting (refer to Section 9 for safety reporting guidelines)
- Concomitant medications documentation
- Collection of fresh tumor sample(s) for subjects who signed the optional portion of the consent.

At any time during the post treatment assessment period, if a subject did not respond to treatment (i.e. CR or PR) or progresses following a response, the subject will proceed directly to the Month 3 visit and be followed for disease outcomes in the long term follow-up period.

7.11.7 Long Term Follow-up Period

All subjects will be followed in the long term follow-up period for survival and disease status if applicable. Subjects will begin the long term follow-up period after they have completed the Month 3 visit of the post treatment assessment period (whether they have responded to treatment or went straight to the month 3 visit due to disease progression)

- Every 3 months (± 2 weeks) through Month 18
- Every 6 months (± 1 month) between Month 24 - Month 60
- Beginning with year 6, Month 72 (± 3 months), subjects will return to the clinic 1 time annually up to 15 years.

The following procedure will be completed at this visit and as outlined in the SOA:

- Physical exam

- **PET-CT Scan**
  - Refer to the imaging charter for detailed instructions.
- Disease assessment
- Labs
  - CBC with differential
  - Anti-KTE-C19 antibodies (refer to Section 7.8)
  - Lymphocyte subsets
  - Anti-CD19 CAR+T cells
  - Replication-competent retrovirus (RCR) analysis
  - Serum samples will also be evaluated for anti-KTE-C19 antibodies, or HAMA, or HABA antibodies for analysis
    - For serum samples that demonstrate increased anti-KTE-C19, or HAMA, or HABA antibodies at the month 3 visit over baseline values, attempts should be made to obtain and test additional serum samples approximately every 3 months until the antibody levels return to baseline (or becomes negative) or up to 1 year from the completion of treatment whichever occurs first.
- Targeted Adverse/**Serious Adverse Event** reporting (**for 24 months** or until disease progression whichever occurs first)
  - Including neurological, hematological, infections, autoimmune disorders, and secondary malignancies until disease progression.
- Targeted concomitant medication documentation (for two years after disease progression)
  - Including gammaglobulin, immunosuppressive drugs, anti-infective, vaccinations, and any therapy for the treatment of progressive diseases

After 24 months results of routine disease assessment per standard of care will be collected. Subjects may also be contacted by telephone to confirm survival status and report targeted adverse events and concomitant medication use (until disease progression). Should a subject require lab collection, labs may be collected at the clinic or at an outside facility to reduce the subject burden.

Should the subject fail to return to the clinic for a scheduled protocol specific visit, sites will need to make 2 attempts by a combination of telephone and mail to contact the subject. Sites must document both attempts to contact the subject. If a subject does not respond within 1 month after the second contact the subject will be considered lost to follow-up and no additional contact will be required.

7.11.8 Retreatment

Subjects who achieved a PR or CR will have an option to receive a second course of conditioning chemotherapy and KTE-C19 if their disease subsequently progresses (and the relapse is not known to be CD19- malignant cells) according to the treating investigator and after consultation and agreement of the Kite Medical Monitor. Subjects should be reconsented including a discussion regarding benefits and risks and carefully explained the need to undergo leukapheresis a second time for the manufacturing of KTE-C19 prior to performing any study related procedures or treatment. This conversation should also be recorded in the subject's source document.

Allowance for retreatment is based on clinical experience reported in the NCI protocol 09-C-0082 where 3 subjects with indolent lymphoma/leukemia experienced durable responses to retreatment after an initial response and disease progression.

To be eligible for a second course of treatment, subjects must be re-evaluated and continue to meet the original study eligibility criteria with the exception of exclusion criteria number **205** and **206** (refer to

Section 5.2) and should not have received subsequent chemotherapy for the treatment of lymphoma. Furthermore, any toxicity related to fludarabine or cyclophosphamide should be stable and resolved to less than grade 1 prior to retreatment with the exception of alopecia. A maximum of 1 retreatment course may occur per subject. **Subjects who are re-treated will follow the same treatment schedule and procedural requirements per the initial treatment.**

Subjects who experience a DLT in phase 1 or a comparable toxicity in phase 2 will not be eligible for retreatment. Furthermore, if a subject has a known neutralizing antibody, the subject will not be eligible for retreatment. However, if a non-neutralizing HAMA or HABA antibody develops, subjects may be retreated if they meet the eligibility criteria.

Schedule of Assessments (1 of 2)

Procedure	Screening (Days before enrollment)	Enrollment	Leukapheresis within approx 5 days after enrollment	Conditioning Chemotherapy Period					IP Administration Period		Post Treatment Follow-up (each visit calculated from Day 0)			
Day	Within 28 days of enrollment			-5	-4	-3	-2	-1	0	1 - 7	Week 2	Week 4 (± **3 days**)	Month 2 (± 1 week)	Month 3 (± 1 week)
Medical history & disease assessment	X													
Physical including weight and ECOG	X													
Mini Mental Status Exam (MMSE)	X								X	QOD [5]		X		X
ECG	X													
LVEF assessment by ECHO	X													
Archival/Fresh tumor to central lab [1]	X											X		
Leukapheresis			X											
Fludarabine/Cyclophosphamide				X	X	X								
KTE-C19 infusion IV									X					
Brain MRI	X													
PET-CT/ disease assessment [2]	X											X		X
Physical exam											X	X	X	X
Vital signs	X		X	X	X	X			X	X	X	X	X	X
Weight	X		X											
Pregnancy test	X													X
Urinalysis	X													
Chemistry panel	X		X	X	X	X			X	X	X	X	X	X
CBC w/differential	X		X	X	X	X			X	X	X	X	X	X
Anti-KTE-C19 antibody [3]			X									X		X
Lymphocyte subsets				X					X			X		X
Blood draw for cytokines				X					X	QOD [5]	X	X		
Blood draw for **anti-CD19** CAR+ T cells [3]									X	Day 7	X	X		X
Blood draw for RCR analysis [4]									X					X
Adverse events/ Concomitant medication	X		→											

[1] Archival tumor sample: Either FFPE tumor block or up to 20 unstained slides. **Fresh tumor sample** for subjects who sign the optional portion of consent, refer to Section 7.9. Archived and fresh tumor (if applicable) samples will only be submitted after eligibility has been confirmed.
[2] PET-CT (Neck-Chest-Abdomen-Pelvis). If PET CT will be > 28 days at the initiation of conditioning chemotherapy, the scans must be repeated to establish a new baseline. Should be completed as close to enrollment as possible.
[3] Blood draw for CAR PCR, on Day 0 prior to administration of T cells; Days 7, 2 weeks, 4 weeks then at 3, 6, 12 and 24 months post T cell infusion Anti-KTE-C19 post 3 month samples, refer to Section 7.8
[4] Blood draw for RCR on Day 0 prior to administration of T cells, harvest and measured at 3, 6 and 12 months; then harvest yearly for up to 15 years and measure if positive at the 12 month visit, or before.
[5] Beginning on day 1 and then every other day through hospitalization

Schedule of Assessments (2 of 2)

Procedure	**Long Term Follow-up Period [1] (Each visit calculated from Day 0)**												
Visit Frequency	Month 6	Month 9	Month 12	Month 15	Month 18	Month 24	Month 30	Month 36	Month 42	Month 48	Month 54	Month 60	Month 72 and Annually Thereafter
Physical exam[1]	X	X	X	X	X	X							
PET-CT (Neck-Chest-Abdomen-Pelvis)[2]	X	X	X	X	X	X							
Disease assessment	X	X	X	X	X	X	X	X	X	X	X	X	X
CBC w/differential [3]	X	X	X	X	X	X							
Anti-KTE-C19 antibody [4]													
Lymphocyte subsets [3]	X	X	X	X	X	X							
Blood draw for anti-CD19 CAR+ T cells [5]	X		X			X							
Blood draw for RCR analysis [6]	X		X			X		X		X		X	X
Targeted AE/SAEs [7]	X	X	X	X	X	X							
Targeted concomitant medication [8]	X	X	X	X	X	X	X	X	X	X	X	X	X

[1] Physical exams will continue through the first 24 months
[2] **PET Scans CTs will continue through Month 24 or until disease progression, whichever comes first**
[3] Subjects will continue to provide samples for CBC w/diffs and lymphocyte subsets through Month 24
[4] Anti-KTE-C19 post 3 month samples, refer to Section 7.8
[5] Blood draw for CAR PCR, on Day 0 prior to administration of T cells; Days 7, 2 weeks, 4 weeks then at 3, 6, 12 and 24 months post T cell infusion
[6] Blood draw for RCR on Day 0 prior to administration of T cells, harvest and measured at 3, 6 and 12 months; then every year for up to 15 years and measure only if positive at the 12 month visit, or before.
[7] **Targeted AEs and SAEs will continue for 24 months or until disease progression (whichever occurs first)**
[8] Targeted concomitant medications will continue until 2 years after disease progression

8 Subject Withdraw

Subjects have the right to withdraw from the study at any time and for any reason without prejudice to their future medical care by the physician or at the institution.

Subjects (or a legally acceptable representative) can decline to continue to receive study required treatment and/or other protocol required procedures at any time during the study but continue to participate in the study. This is referred to as partial withdrawal of consent.

If partial withdrawal of consent occurs, the investigator must discuss with the subject the appropriate process for discontinuation from investigational product, study treatment or other protocol required therapies and must discuss options for continued participation, completion of procedures and the associated data collection as outlined in the SOA. The level of follow-up and method of communication should also be discussed between the research staff and the subject and documented in the source documents.

Withdraw of full consent for a study means that the subject does not wish to receive further protocol required therapy or undergo procedures and the subject does not wish to continue further study follow-up. Subject data collected up to withdraw of consent will be retained and included in the analysis of the study, and where permitted, publically available data (death records) can be included after withdrawal of consent (Guidance for Sponsors, Clinical Investigators, and IRBs Data Retention When Subjects Withdraw from FDA-Regulated Clinical Trials, 2008). The investigator is to discuss with the subject appropriate procedures for withdrawal from the study.

As part of the study sites may be asked to conduct searches of public records, such as those establishing survival status, if available, to obtain survival data for any subject for whom the survival status is not known. Sites may be also asked to also retrieve autopsy reports to confirm status of disease at the time of death.

The investigator and/or sponsor can also decide to withdraw a subject from the investigational product and/or other protocol-required therapies, protocol procedures, or the study as a whole or at any time prior to study completion.

8.1 Reasons for Removal from Treatment

Reasons for removal from protocol required investigational products or procedures include any of the following:

- Adverse Event
- Subject request/non-compliance
- Product not available
- Lost to Follow-up
- Death
- Decision by sponsor

8.2 Reasons for Removal from Study

Reasons for removal of a subject from the study are as follows:

- Subject withdrawal of consent from further follow-up
- Investigator decision
- Lost to follow-up
- Death

9 Safety Reporting

9.1 Adverse Events

An adverse event is defined as any untoward medical occurrence in a clinical trial subject. The event does not necessarily have a relationship with study treatment. The investigator is responsible for ensuring that any adverse events observed by the investigator or reported by the subject are recorded in the subject's medical record.

The definition of adverse events includes worsening of a pre-existing medical condition. Worsening indicates that the pre-existing medical condition has increased in severity, frequency, and/or duration or has an association with a worse outcome. A pre-existing condition that has not worsened during the study or involves an intervention such as elective cosmetic surgery or a medical procedure while on study, is not considered an adverse event

Interventions for pretreatment conditions (such as elective cosmetic surgery) or medical procedures that were planned before study participation are not considered adverse events. Hospitalization for study treatment infusions or precautionary measures per institutional policy are not considered adverse events.

The term "disease progression" as assessed by measurement of malignant lesions on radiographs or other methods should not be reported as adverse events. Death due to disease progression in the absence of signs and symptoms should be reported as the primary tumor type (e.g. DLBCL).

For situations when an adverse event or serious adverse event is due to the disease under investigation report the signs and symptoms. Worsening of signs and symptoms of the malignancy under study should also be reported as adverse events in the appropriate section of the CRF.

The investigators clinical judgment is used to determine whether a subject is to be removed from treatment due to an adverse event. In the event of a subject or subject's legally acceptable representative requests to withdraw from protocol required therapies or the study due to an adverse event, the subject should undergo the procedures outlined in the Month 3 visit of the SOA.

If a subject begins a new anticancer therapy, the adverse event reporting period for non-serious adverse events ends at the time the new treatment is started.

9.2 Reporting of Adverse Events

The investigator is responsible for ensuring that all adverse events observed by the investigator or reported by the subject that occur after signing of the consent through 3 months after treatment with KTE-C19 infusion are monitored and reported. After 3 months, the investigator will be asked to monitor and report targeted adverse events including neurological, hematological, infections, autoimmune disorders, and secondary malignancies for 24 months or until disease progression whichever occurs first)

For subjects who do not receive KTE-C19, the reporting period ends 30 days after the last dose of the conditioning chemotherapy.

The investigator must address the below adverse events:

- Adverse event diagnosis or syndrome (if not known, signs or symptoms)
- Dates of onset and resolution
- Severity
- Assessment of relatedness to investigational product, conditioning chemotherapy or study procedures
- Action taken

Adverse event grading scale used will be the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. A copy of the grading scale can be downloaded from the CTEP home page (http://ctep.cancer.gov). **Cytokine Release Syndrome events will be reported using the grading scale outlined in table 11 of Section 6.4.4.**

In reviewing adverse events, investigators must assess whether the adverse event is possibly related to 1) the investigational product (KTE-C19), 2) conditioning chemotherapy or 3) any protocol required study procedure. The relationship is indicated by a yes or no response and entered into the CRF. A yes response should indicate that there is evidence to suggest a causal relationship between the study treatment or procedure and the adverse event. Additional relevant data with respect to describing the adverse event will be collected in the CRFs.

The investigator is responsible for reviewing laboratory test results and determining whether an abnormal value in an individual study subject represents a clinically significant change from the subject's baseline values. Abnormal laboratory findings without clinical significance (based on investigators assessment) are not to be recorded as adverse events. Where applicable, clinical sequelae (not the laboratory abnormality) are to be recorded as the adverse event.

The investigator is expected to follow reported adverse events until stabilization or resolution.

9.3 Definition of Serious Adverse Events

The investigator is responsible for reporting all serious adverse events observed by the investigator or reported by the subject that occur after signing of the consent through 3 months after the KTE-C19 infusion. After 3 months, **serious targeted adverse events** observed by the investigator or reported by the subject will be reported for 24 months or until disease progression whichever occurs first). For subjects who do not receive KTE-C19, the reporting period ends 30 days after the last dose of conditioning chemotherapy.

A serious adverse event is defined as an adverse event that meets at least 1 of the following serious criteria:

- Fatal
- Life threatening (places the subject at immediate risk of death)
- Requires in patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Congenital anomaly/birth defect
- Other medically important serious event

An adverse event would meet the criterion of "requires hospitalization" if the event necessitated an admission to a health care facility (e.g., overnight stay).

Events that require an escalation of care when the subject is already hospitalized should be recorded as a serious adverse event. Examples of such events include movement from routine care in the hospital to the ICU or if that event resulted in a prolongation of the existing planned hospitalization. The event should be documented in the CRFs with the highest degree of severity that resulted in the hospitalization extension.

If an investigator considers an event to be clinically important, but it does not meet any of the serious criteria, the event could be classified as a serious adverse event with the criterion of "other medically important serious event."

9.4 Reporting of Serious Adverse Events and Non-Serious CRS events grade ≥3

All serious adverse events and **non-serious CRS events grade ≥ 3 (Lee 2014; Table 11)** must be submitted to Theorem Global Safety Advantage within 24 hours following the investigators knowledge of the event. All serious adverse events will be submitted by fax (Fax: 866-869-1551) or email drugsafety@Theoremclinical.com.

SAEs and **non-serious CRS events grade ≥ 3** may be reported by phoning GSA at 877-324-8200, however a phone call alone is insufficient; all events must be reported using a SAE Report Form (Appendix B) submitted by fax or email within the time frames described in the protocol. **Subsequently, all SAEs will be reported to the FDA per 21 CFR312.32.**

Progression of the malignancy during the study should not be reported as a serious adverse event. Adverse events associated with disease progression may be reported as serious adverse event. If the malignancy has a fatal outcome within 3 months of the last day of the conditioning therapy or KTE-C19 then the event leading to death must be recorded as a serious adverse event with CTC grade 5.

Death must be reported if it occurs during the serious adverse event reporting period, irrespective of any intervening treatment.

Any death occurring after the first dose of chemotherapy, for the purpose of pre-conditioning, and within 3 months of the KTE-C19 infusion, regardless of attribution to treatment, requires expedited reporting within 24 hours. Any death occurring greater than 3 months after the KTE-C19 infusion requires expedited reporting within 24 hours only if it is considered related to treatment.

9.5 Pregnancy and Lactation

There is no relevant clinical experience with KTE-C19 in pregnant or lactating women, and animal reproductive studies have not been performed. Women of child bearing potential must have a negative pregnancy test prior to enrollment because of the potentially dangerous effects of the preparative chemotherapy on the fetus. This experimental therapy should not be administered to pregnant women or women who are breastfeeding.

If a pregnancy occurs in a female subject enrolled into the study, or a female partner of a male subject within 6 months of completing the KTE-C19 infusion, the pregnancy must be reported to the key sponsor contact.

In addition to reporting any pregnancies occurring during the study, investigators should monitor for pregnancies that occur after the last dose of KTE-C19 through 6 months for female subjects and for 6 months for the female partner of the male subjects.

The pregnancy should be reported to the key sponsor contact within 24 hours of the investigators knowledge of the pregnancy event.

If a lactation case occurs while the female subject is taking protocol required therapies report the lactation case to the key sponsor contact.

In addition to reporting a lactation case during the study, investigators should monitor for lactation cases that occur after the last dose of protocol required therapies through 6 months

Any lactation case should be reported to the key sponsor contact within 24 hours of the investigator's knowledge of the event.

9.6 Safety Review Team and Dose-Limiting Toxicity

The SRT will be specifically chartered to review safety data during phase 1 of the study and make a recommendation to progress the study from phase 1 to phase 2 based on the incidence of KTE-C19 DLT and review of serious adverse events.

Dose-limiting toxicity is defined as the following KTE-C19-related events with onset within the first 30 days following KTE-C19 infusion:

- Grade 4 neutropenia lasting longer than 21 days from the day of cell transfer
- Grade 4 thrombocytopenia lasting longer than 35 days from the day of cell transfer
- All other grade 3 toxicities lasting more than 3 days (including grade 3 hypotension requiring the use of pressors) and all grade 4 toxicities, with the exception of the following conditions which are not considered DLT's:
    - Aphasia/dysphasia or confusion/cognitive disturbance which resolves to grade 1 or less within 2 weeks and to baseline within 4 weeks
    - Fever grade 3
    - Myelosuppression (includes bleeding in the setting of platelet count less than 50 $x10^9$/L and documented bacterial infections in the setting of neutropenia), defined as lymphopenia, decreased hemoglobin, neutropenia and thrombocytopenia unless neutropenia and thrombocytopenia meet the DLT definition described above
    - Immediate hypersensitivity reactions occurring within 2 hours of cell infusion (related to cell infusion) that are reversible to a grade 2 or less within 24 hours of cell administration with standard therapy
    - Hypogammaglobulinemia grade 3 or 4
    - **Any KTE-C19-related adverse event requiring intubation, including grade 4 confusion requiring intubation for airway protection is considered to be a DLT.**

During phase 1 of the study, 6 subjects will be enrolled and receive at a target dose of 2 x 10^6 anti-CD19 CAR+ T cells/kg (± 20%) and subsequently be evaluated for DLTs within the first 30 days following the completion of their respective KTE-C19 infusion. The analysis of DLTs will be based on the DLT evaluable set as defined in Section 10.5 Should ≤ 1 of the 6 subjects present with a protocol defined DLT, the SRT should recommend to proceed to phase 2 of the trial. If review of the first 5 subjects indicates no DLT, the study may proceed to phase 2.

However, if **2** of the 6 enrolled subjects present with a protocol defined DLT during phase 1, the SRT may recommend enrolling 2 additional sets of 3 subjects (up to 12 subjects in total) at the same dose that was administered in the first 6 subjects. In this scenario, progression to phase 2 of the study will proceed if ≤ 2 of the first 9 or if ≤ 3 of the 12 subjects present with a DLT. If the initial regimen is not safe, a lower dose of 1 x 10^6 anti-CD19 CAR+ T cells/kg may be evaluated in an additional 6-12 subjects.

9.7 Data Safety Monitoring Board

An independent Data Safety Monitoring Board (DSMB) will meet 2 times during the phase 2 portion of the study when 20 and 50 subjects enrolled into cohort 1 have completed their 3 month disease assessment. In addition, the DSMB Chair will review reported serious adverse events monthly. The DSMB will review safety and efficacy data and be chartered to make trial conduct recommendations based on an analysis of risk vs. benefit.

10 Statistical Considerations

10.1 Hypothesis

This study is designed to differentiate between a treatment that has a true response rate of 20% or less and a treatment with a true response rate of 40% or more. The hypothesis is that the objective response rate to KTE-C19 in the DLBCL cohort and in the overall study population is significantly greater than 20%.

10.2 Study Endpoints

10.2.1 Primary

Phase 1: Incidence of adverse events defined as dose-limiting toxicities (DLT)

Phase 2: Objective Response Rate: ORR is defined as the incidence of either a complete response or a partial response by the revised IWG Response Criteria for Malignant Lymphoma (Cheson 2007). All subjects that do not meet the criteria for an objective response by the analysis cutoff date will be considered non-responders.

10.2.2 Secondary

Objective response rate among subjects in phase 1 will be summarized.

Duration of Response: DOR for subjects who experience an objective response, DOR is defined as the date of their first objective response which is subsequently confirmed to disease progression per the revised IWG Response Criteria for Malignant Lymphoma (Cheson 2007) or death regardless of cause. Subjects not meeting the criteria for progression or death by the analysis data cutoff date will be censored at their last evaluable disease assessment date and their response will be noted as ongoing.

Progression Free Survival: PFS is defined as the time from the KTE-C19 infusion date to the date of disease progression per the revised IWG Response Criteria for Malignant Lymphoma (Cheson 2007) or death from any cause. Subjects not meeting the criteria for progression by the analysis data cutoff date will be censored at their last evaluable disease assessment date.

Overall Survival: OS is defined as the time from KTE-C19 infusion to the date of death. Subjects who have not died by the analysis data cutoff date will be censored at their last contact date.

Incidence of adverse events and clinical significant changes in safety lab values.

Incidence of anti-KTE-C19 antibodies, levels of anti-CD19 CAR+ T cells in blood and levels of cytokines in serum will be summarized.

10.2.3 Exploratory Endpoints

Objective Response Rate and duration of second response among subjects retreated with KTE-C19 (Section 7.11.8)

Investigation of potential biomarker development based on assessment of blood cells, tumor cells and the proposed actions of the investigational product.

10.3 Sample Size Considerations

The anticipated enrollment in this study is approximately 118 to 124 subjects.

Six to 12 subjects will be enrolled into phase 1 of this study.

If the study proceeds to phase 2, 72 subjects will be enrolled into cohort 1 and up to 40 subjects will be enrolled into cohort 2.

The primary efficacy endpoint and all analyses based on the objective response (objective response, duration of response, progression-free survival) in the phase 1 and phase 2 portions of the study will be based on a modified intent to treat (mITT) population consisting of all subjects who receive the planned **dose** of KTE-C19.

This study uses a single arm design to test for an improvement in response rate in the DLBCL cohort (approximately n=72) and in the overall study population (cohorts 1 and 2 combined; n=112). For the test of efficacy this study has ≥ 90% power to distinguish between an active therapy with a 40% true response rate from a therapy with a response rate of 20% or less with a 1-sided alpha level of 0.025.

The overall 1-sided alpha level of 0.025 will be divided between the inference on cohort 1 and the inference in the overall study population using the methodology described in Song, 2007 and Wang, 2007. The objective response for cohort 1 will be tested at a 1-sided alpha level of 0.022 and the objective response in the overall study population will be tested at a 1-sided alpha level of 0.0075.

Within cohort 1, 2 interim and 1 primary analyses will be performed.

- Interim analysis 1 will be conducted after 20 subjects in the mITT set have been evaluated for response 3 months after the KTE-C19 infusion. This interim analysis will be for futility only. If more than or equal to 5 responses are observed in the first 20 subjects, accrual to phase 2 will continue to the planned 112 subjects. Under the null hypothesis, the likelihood of stopping for futility at this analysis is 63%.
- Interim analysis 2 will be conducted after 50 subjects have been evaluated for response 3 months after the KTE-C19 infusion. This interim analysis will assess early demonstration of efficacy. Under the alternative hypothesis, the likelihood of achieving the criteria for early efficacy is 84%.
- The primary analysis of cohort 1 will occur after all subjects in cohort 1 have been assessed for response 6 months after the KTE-C19 infusion.

An alpha spending function will be used to allocate the alpha level between interim analysis 2 of cohort 1 and the primary analysis of cohort 1. Using the Lan-DeMets family of alpha spending functions with a Pocock boundary, the nominal 1-sided alpha used to test for efficacy at interim analysis 2 of cohort 1 is 0.017. Using this boundary, the criteria for early efficacy may be met if 17 or more patients in the 50 evaluated at interim analysis 2 respond. Otherwise, the planned primary analysis of cohort 1 will occur when all subjects enrolled into cohort 1 have been assessed for response 6 months after the KTE-C19 infusion. At the primary analysis (n=72 subjects), a statistically significant improvement in response will be determined if 23 or more subjects respond. Inferential analyses of the overall study population (including cohort 2) will not be performed at interim analysis 1 or 2 of cohort 1. Accrual to the study will continue during interim analysis 1 and interim analysis 2 of cohort 1.

Within the overall study population, 1 primary analysis will be performed when all subjects accrued to cohorts 1 and 2 have been assessed for response 6 months after the KTE-C19 infusion. This testing will be performed at a 1-sided alpha level of 0.0075. For the targeted enrollment of 112 subjects in the overall study population (72 subjects in cohort 1 and up to 40 subjects in cohort 2), 34 or more responses must be observed in order to determine a statistically significant improvement in response. Descriptive confidence intervals about the objective response rates within cohorts 1 and 2 will be presented with the inferential analysis of the overall study population.

Enrollment of up to 40 subjects into cohort 2 is targeted, however, given the low prevalence of refractory PMBCL and TFL, fewer than 40 subjects may actually be enrolled. If at least 20 but fewer than 40 subjects are accrued to cohort 2, the minimum number of subjects with response that must be observed in order to determine a statistically significant improvement in response ranges from 29 to 34 (Table 13). If less than 20 subjects are enrolled into cohort 2, the analysis of the overall study population will be descriptive and would occur no later than 2 years after completion of accrual into cohort 1.

This procedure preserves the designated alpha level (1-sided) of 0.025 and has ≥ 90% power. Simulation (10000 replicates) via R version 3.1.0 and EAST version 6.3 were used to evaluate the operating characteristics of this design.

Table 13. Minimum number of responders required to determine statistical significance in the overall study population

Subjects enrolled in cohort 2	Subjects enrolled in study	Minimum number of responders required to determine statistical significance in the overall study population
20	92	29
21	93	29
22	94	30
23	95	30
24	96	30
25	97	30
26	98	31
27	99	31
28	100	31
29	101	31
30	102	32
31	103	32
32	104	32
33	105	32
34	106	33
35	107	33
36	108	33
37	109	33
38	110	34
39	111	34
40	112	34

10.4 Statistical Assumptions

This study assumes that the underlying response rate (in the absence of treatment with investigational therapy) is 20%. In order to evaluate the validity of this assumption, retrospective studies (historical data and database reviews) of the response rate in the study target patient population will be conducted. The DSMB will be provided with the results of these retrospective studies and may recommend modifying the study hypothesis and statistical criteria if the retrospective studies indicate the assumption of a 20% underlying response rate is not supported by historical data. Any DSMB evaluation and recommendation regarding this assumption will occur prior to the planned futility analysis.

10.5 Analysis Subsets

Modified Intent to Treat Set (mITT): the modified intent to treat set will consist of all subjects enrolled and treated with the planned **dose** of KTE-C19. This analysis set will be used for all analyses of objective response and endpoints based on objective response (objective response, duration of response, progression-free survival) for both the phase 1 and phase 2 portions of the study.

KTE-C19 will be administered as a single infusion at a target dose of 2 x 10^6 anti-CD19 CAR+ T cells/kg (± 20%). A minimum dose of 1 x 10^6 anti-CD19 CAR+ T cells/kg may be administered. For subjects weighing greater than 100 kg, a maximum flat dose of 2 x 10^8 anti-CD19 CAR+ T cells will be administered.

DLT evaluable set (phase 1 only) will include subjects treated in the phase 1 portion of the study who:

- received the target and were followed for at least 30 days after the anti-CD19 CAR + T cell infusion; or
- received a dose of anti-CD19 CAR + T cells lower than the upper target (eg ≤ 2.4 x 10^6 anti-CD19 CAR+ T cells/kg) and experienced a DLT during the 30 day post-infusion period.

If needed, more subjects will be enrolled to achieve 6 DLT evaluable subjects at a target dose of 2 x 10^6 anti-CD19 CAR+ T cells/kg (± 20%).

Safety set: the safety set is defined as all subjects treated with any dose of KTE-C19.

10.6 Access to Individual Subject Treatment Assignments

This is a single arm, open-label study and subjects and investigators will be aware of treatment received. Data handling procedures for the phase 2 portion of the study will be devised to reduce potential sources of bias and maintain the validity and credibility of the study. These procedures will be outlined in the study statistical analysis plan, DSMB charter, and Trial Integrity Document.

10.7 Interim Analysis

10.7.1 Interim Analysis and Early Stopping Rules

The SRT will be chartered to review safety during phase 1 of the study only and make a recommendation to progress the study from phase 1 to phase 2 based the incidence of DLT.

An independent DSMB will be formed to review accumulating safety and efficacy data 2 times during the phase 2 portion of the study, when 20 and 50 subjects enrolled into cohort 1 have completed their 3 month disease assessment.

10.7.2 Safety Interim Analysis

The DSMB will review AE and SAE information on a regular basis throughout subject treatment in phase 2 of the study. The DSMB may request additional safety data or modifying the study conduct. The sponsor may request additional reviews by the DSMB if safety concerns are identified. Data submitted to the DSMB may be monitored or unmonitored to facilitate and ensure timely DSMB review.

10.7.3 Efficacy Interim Analysis

Within cohort 1, 2 interim analyses will be performed.

- Interim analysis 1 will be conducted after 20 subjects in the mITT set have been evaluated for response 3 months after the KTE-C19 infusion. This interim analysis will be for futility only. If more than or equal to 5 responses are observed in the first 20 subjects, accrual to phase 2 will continue to the planned 112 subjects. Under the null hypothesis, the likelihood of stopping for futility at this analysis is 63%.
- Interim analysis 2 will be conducted after 50 subjects have been evaluated for response 3 months after the KTE-C19 infusion. This interim analysis will assess early stopping for efficacy. Under the alternative hypothesis, the likelihood of achieving the criteria for early efficacy is 84%.

An alpha spending function will be used to allocate the alpha level between interim analysis 2 of cohort 1 and the primary analysis of cohort 1. Using the Lan-DeMets family of alpha spending functions with a Pocock boundary, the nominal 1-sided alpha used to test for efficacy at interim analysis 2 of cohort 1 is 0.017. Using this boundary, the criteria for early efficacy may be met if 17 or more patients in the first 50 evaluated at interim analysis 2 respond. Otherwise, the planned primary analysis of cohort 1 will occur when all subjects enrolled into cohort 1 have been assessed for response 6 months after the KTE-C19 infusion.

10.8 Planned Method of Analysis

The primary efficacy analyses of cohort 1 will be performed when the last enrolled subject into cohort 1 has had the opportunity to be evaluated for response 6 months after the KTE-C19 infusion. The primary analysis of the overall study population will be performed when the last enrolled subject into either study cohort has had the opportunity to be evaluated for response at 6 months after the planned KTE-C19 infusion. Additional analyses may occur after the primary analysis of cohort 1 and after the overall study population have been completed. These additional analyses will be descriptive and will occur after inferential testing has been performed. The final analysis will occur when all subjects have completed the study. If less than 20 subjects are enrolled into cohort 2, the analysis of the overall study population will be descriptive and would occur no later than 2 years after completion of accrual into cohort 1.

The primary endpoint of objective response rate for all analyses (futility, interim, and primary) will be based on investigator review of disease assessments in the miTT set. Sensitivity analyses of objective response rate based on central radiologic review of disease assessments may be performed.

Analyses of efficacy endpoints will be summarized by study phase, cohort, and overall. Analyses of safety endpoints will be evaluated by cohort and overall.

10.8.1 Objective Response Rate

The incidence of objective response and exact 2-sided 95% confidence intervals will be generated. An exact binomial test will be used to compare the observed response rate to a response rate of 20%.

10.8.2 Duration of Response

Kaplan-Meier estimates and 2-sided 95% confidence intervals will be generated for duration of response.

10.8.3 Progression Free Survival

Kaplan-Meier estimates and 2-sided 95% confidence intervals will be generated for progression-free survival time.

10.8.4 Overall Survival

Kaplan-Meier estimates and 2-sided 95% confidence intervals will be generated for OS.

10.8.5 Safety

Subject incidence rates of adverse events including all, serious, fatal, CTCAE version 4 grade 3 or higher and treatment related AEs reported throughout the conduct of the study will be tabulated by system organ class. Changes in laboratory values and vital signs will be summarized with descriptive statistics. The incidence of concomitant medications will be summarized.

Tables and/or narratives of deaths though the long term follow-up and treatment related SAEs will be provided.

10.8.6 Long Term Data Analysis

All subjects will be followed for survival for up to approximately 15 years after the last subject is enrolled. No formal hypothesis testing will be performed based on data obtained after the cutoff for the primary analysis. Descriptive estimates of key efficacy and safety analyses may be updated to assess the overall treatment profile.

11 Regulatory Obligations

11.1 Independent Review Board /Independent Ethics Committee

A copy of the protocol, ICF and any additional subject or trial information such as subject recruitment materials must be submitted to each sites respective IRB/IEC for approval. Once approval is obtained from the IRB/IEC, all documents must be provided to the key sponsor contact before subject recruitment can begin.

The investigator must also receive IRB/IEC approval for all protocol and ICF changes or amendments. Investigators must ensure that ongoing/continuous IRB/IEC approval (i.e. annual approval) is provided throughout the conduct of the study. Copies of IRB/IEC approval are to be forwarded to the key sponsor contact for archiving.

During the course of the study, investigators are to submit site specific and study serious adverse events (provided to the site by the key sponsor contact) along with any protocol deviations to their IRB/IEC in accordance with their respective IRB/IEC policies.

11.2 Subject Confidentiality

Subject confidentiality must be contained at all material submitted to the key sponsor contact. The following rules are to be applied.

- Subjects will be identified by a unique identification number
- Date of birth will be reported according with local laws and regulations

- Age at the time of enrollment

For reporting of serious adverse events, subjects will be identified by their respective subject identification number, initials and data of birth (as per their local reporting requirements for both initials and date of birth)

Per federal regulations and ICH/GCP guidelines, investigators and institutions are required to permit authorization to the sponsor, CRO, IRB/IEC and regulatory agencies to subject's original source documents for verification of study data. The investigator is responsible for informing potential subjects that such individuals will have access to their medical records which includes personal information.

11.3 Investigator Signatory Obligations

Each clinical study report will be signed by the coordinating investigator. The coordinating investigator will be identified by Kite Pharma under the following criteria:

- A recognized expert in the disease setting
- Provided significant contributions to the design or analysis of study data
- Participate in the study and enrolled a high number of eligible subjects

12 Protocol Amendments and Termination

If the protocol is amended, the investigators agreement with the amendment and the IRB/IEC approval of the amendment must be obtained. Documentation acknowledging approval from both parties are to be submitted to the key sponsor contact

Kite Pharma reserves the right to terminate the study at any time. Both Kite pharma and the investigator reserve the right to terminate the investigators participation in the study as per the terms of the agreement in the study contract. The investigator is to provide written communication to the IRB/IEC of the trial completion or early termination and provide the CRO with a copy of the correspondence.

Kite Pharma reserves the unilateral right, at is sole discretion, to determine whether to manufacture KTE-C19 T cells and provide them to sites and subjects after the completion of the study and before treatment becomes commercially available.

13 Study Documentation and Archive

The investigator will maintain a list of qualified staff to whom study responsibilities have been delegated. These individuals authorized to fulfil these responsibilities should outlined and included in the Delegation of Authority Form.

Source documents are original documents, data and records for which the study data are collected and verified. Example of such source documents may include, but are not limited to, hospital records and patient charts, laboratory, pharmacy, radiology and records, subject diaries, microfiches, correspondence and death registries. Case report form entries may be considered as source data if the site of the original data collection is not available. However use of the CRFs as source documentation as a routine practice is not recommended.

The investigator and study staff are responsible for maintaining a comprehensive and centralize filing system of all subject records that are readily retrieved to be monitored and or audited at any time by the key sponsor contact, regulatory authorities and IRB/IECs. The filing system will include at minimum:

- Subject content including ICFs and subject identification lists

- Protocols and protocol amendments, investigator brochure, copies of pre-study documentation, and all IRB/IEC and sponsor communication
- Proof of receipt, experimental treatment flow records and experimental product related correspondence.

Original source documents supporting entries into CRFs must be maintained at the site and readily available upon request. No study documents should be discarded without prior written agreement between Kite Pharma and the investigator. Should storage no longer be available to archive source documents or must be moved to an alternative location, the research staff should notify the key sponsor contact prior to the shipping the documents.

14 Study Monitoring and Data Collection

The key sponsor contact, monitors, auditors or regulatory inspectors are responsible for contacting and visiting the investigator for the purpose of inspecting the facilities and verifying source documents and records assuring that subject confidentially is respected.

The monitor is responsible for source document verification of CRF data at regular intervals during the study. Protocol adherence, accuracy and consistency of study conduct and data collection with respect to local regulations will be confirmed. Monitors will have access to subject records as identified in Section 13.

By signing the investigator agreement, the investigator agrees to cooperate with the monitor to address and resolve issues identified during monitoring visits.

In accordance with ICH GCP and the audit plan, a site may be chosen for a site audit. A site audit would include, but is not limited to, an inspection of the facility (ies), review of subject and study related records, and compliance with protocol requirements as well as ICH GCP and applicable regulatory policies.

All data will be collected in an electronic CRF system. All entries must be completed in English and concomitant medications should be identified by tradenames. For further details surrounding the completion of CRFs, please refer to the CRF completion guidelines.

15 Publication

Authorship of publications from data generated in study KTE-C19-101 will be determined based on the uniform requirements for manuscripts submitted to biomedical journals (as outlined in the International Committee of Medical Journal Editors December 2013) which states:

- Authorship should be based on
  - Substantial contributions to the conception or design of the work, acquisition of data, analysis, or interpretation of data for the work AND
  - Drafting the article or revising it critically for important intellectual content; AND
  - Final approval of the version to be published; AND
  - Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work re appropriately investigated or resolved

When a large, multicenter group has conducted the work, the group should identify the individuals who accept direct responsibility for the manuscript. This individual should fully meet the criteria for authorship defined above.

Funding, collection of data or general supervision of the research alone or in combination does not qualify an individual for authorship.

Any publication, in any form, that is derived from this study must be submitted to Kite Pharma for review and approval. The study contract between the institution, principal investigation and Kite Pharma or its delegate will outline the requirements for publication review.

16 Compensation

Kite Pharma will provide compensation for study related illness or injury pursuant to the information outlined in the injury section of the ICF.

References

Ardeshna KM, Kakouros N, Qian W, et al. Conventional second-line salvage chemotherapy regimens are not warranted in patients with malignant lymphomas who have progressive disease after first-line salvage therapy regimens. *Br J Haematol.* 2005 Aug;130(3):363-72.

Armandi P, Welch S, Kim HT, et al. Prognostic factors for patients with diffuse large B cell Lymphoma and transformed indolent lymphoma undergoing autologous stem cell transplant in the positron emission tomography era. British Journal of Haematology. 2013;16o:608-617

Better M, Pugach, O, et al Rapid cell expansion (RACE) technology for production of engineered autologous T-cell therapy: Path toward manageable multicenter clinical trials in aggressive NHL with anti-CD19 CAR. ASCO 2014 Chicago, Illinios. Poster Presentation; #3079

Blanc V, Bousseau A, Caron A, et al. SAR3419:an anti-CD19-maytansinoid immunoconjugate for the treatment of B-cell malignancies. Clin Cancer Res 2011;17:6448–6458.

Cheson BD, Pfistner B, Juweid ME, Gascoyne RD, Specht L, Horning SJ, et al. Revised response criteria for malignant lymphoma. *J Clin Oncol.* 2007;25(5):579

Coiffier B, Lepage E, Brière J, et al. CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large B-cell lymphoma. *N Eng J Med* 2002;346(4):235–242.

Coiffier B, Gisselbrecht C, Bosly A, et al. Ten years' followup of the LNH98.5 study, first randomized study comparing R-CHOP to CHOP chemotherapy in patients with diffuse large B-cell lymphoma. A GELA study. Program and abstracts of the 51st American Society of Hematology Annual Meeting; December 5–8, 2009; New Orleans, Louisiana: Abstract 3741 (poster).

Davila ML et al. Efficacy and Toxicity Management of 1928z CAR T Cell Therapy in B Cell Acute Lymphoblastic Leukemia. Sci Transl Med. Feb 2014 19;6(224):224ra25.

Dunleavy K, Pittaluga S, Maeda LS, et al. Dose-Adjusted-EPOCH-R Therapy in Primary Mediastinal B-cell Lymphoma. *N Eng J Med*. April 11, 2013

Fayad L, Offner F, Smith MR, Safety and Clinical Activity of a Combination Therapy Comprising Two Antibody-Based Targeting Agents for the Treatment of Non-Hodgkin Lymphoma: Results of a Phase I/II Study Evaluating the Immunoconjugate Inotuzumab Ozogamicin With Rituximab J Clin Oncol 31:573-583.

Gisselbrecht, C et al 2010. Salvage regimens with autologous transplantation for relapsed large B-cell lymphoma in the rituximab era. J Clin Oncol 28: 4184-90.

Guidance for Sponsors, Clinical Investigators, and IRBs Data Retention When Subjects Withdraw from FDA-Regulated Clinical Trials, 2008 http://www.fda.gov/Drugs/default.htm Published October 2008, Accessed June 27, 2014.

Hitz F, Connors JM, Gascoyne RD, Outcome of Patients with Chemotherapy Refractory and Early Progressive Diffuse Large B Cell Lymphoma After R-CHOP Treatment; *Blood* (ASH Annual Meeting Abstracts, Poster Session) 2010 116: Abstract 1751

Josting A, et al. Prognostic factors and treatment outcome in primary progressive Hodgkins Lymphoma: a report from the German Hodgkin study group; *Blood* 2000 August 15; 96: 1280-1286.

Kershaw MH, Westwood AJ, Darcy PK. Gene-engineered T cells for cancer therapy. *Nature Reviews Cancer.* 13;525-541 (2013)

Kochenderfer JN et al. Construction and Pre-clinical Evaluation of an Anti-CD19 Chimeric Antigen Receptor. J Immunother. 2009 September; 32(7): 689–702.

KochenderferJN et al Adoptive transfer of syngeneic T cells transduced with a chimeric antigen receptor that recognizes murine CD19 can eradicate lymphoma and normal B cells. Blood. Nov 11, 2010a; 116(19): 3875–3886.

Kochenderfer JN, Wilson WH, Janik JE, Dudley ME, Stetler-Stevenson M, Feldman SA, Maric I, Raffeld M, Nathan DA, Lanier BJ, Morgan RA, Rosenberg SA. Eradication of B-lineage cells and regression of lymphoma in a patient treated with autologous T cells genetically engineered to recognize CD19. Blood. 2010b Nov 18; 116(20): 4099-102.

Kochenderfer JN et al. B-cell depletion and remissions of malignancy along with cytokine-associated toxicity in a clinical trial of anti-CD19 chimeric-antigen-receptor–transduced T cells. Blood 2012 119:2709-2720.

Kochenderfer JN et al. Effective Treatment of Chemotherapy-Refractory Diffuse Large B-Cell Lymphoma with Autologous T Cells Genetically-Engineered To Express An Anti-CD19 Chimeric Antigen Receptor. Blood. November 15, 2013 vol. 122 no. 21 168.

Kochenderfer et al. Chemotherapy-Refractory Large-cell and Indolent B-cell Malignancies Can Be Effectively Treated with Autologous T Cells Expressing Anti-CD19 Chimeric Antigen Receptor. *J Clin Oncol*. 2014. pii: JCO.2014.56.2025

Kowolik CM, Topp MS, Gonzalez S, et al. CD28 costimulation provided through a CD19-specific chimeric antigen receptor enhances in vivo persistence and antitumor efficacy of adoptively transferred T cells. *Cancer Res* 66(22):10995-11004, 2006

Kuruvilla, J et al. Salvage chemotherapy and autologous stem cell transplantation are inferior for relapsed or refractory primary mediastinal large B-cell lymphoma compared with diffuse large B-cell lymphoma; 2008, Vol. 49, No. 7 , Pages 1329-1336 (doi:10.1080/10428190802108870)

Lan-Demets/Pocock: KK Gordon Lan and David L. DeMets, Discrete sequential boundaries for clinical trials, Biometrika, 983; 70:3:659-663.

Lee DW, Gardner R, Porter DL, et al. How I treat: current concepts in the diagnosis and management of cytokine release syndrome. Blood. 2014 May 29. pii: blood-2014-05-552729.

Matasar MJ, Czuczman MS, Rodriguez MA, et al. Ofatumumab in combination with ICE or DHAP chemotherapy in relapsed or refractory intermediate grade B-cell lymphoma. *Blood.* 2013 Jul 25;122(4):499-506

Moye LA, Deswal A. Trials within trials: confirmatory subgroup analyses in controlled clinical experiments, Controlled Clinical Trials, 2001; 22:605-619

Nagle SJ, Woo K, Schuster SJ, et al. Outcomes of patients with relapsed/refractory diffuse large B-cell lymphoma with progression of lymphoma after autologous stem cell transplantation in the rituximab era. *Am J Hematol*. 2013 Oct;88(10):890-4.

National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology; Non-Hodkin's Lymphomas, Version 1.2014. http://www.nccn.org/professionals/physician_gls/f_guidelines.asp#nhl Accessed January 22, 2014.

Nicholson IC, Lenton KA, Little DJ, et al. Construction and characterisation of a functional CD19 specific single chain Fv fragment for immunotherapy of B lineage leukaemia and lymphoma. Mol Immunol 1997, 34(16–17):1157-1165

Philip T, Guglielmi C, Hagenbeek A, et al. Autologous bone marrow transplantation as compared with salvage chemotherapy in relapses of chemotherapy-sensitive non-Hodgkin's lymphoma. *N Engl J Med* 1995; 333: 1540-5.

Savage KJ, Al-Rajhi N, Voss N et al. Favorable outcome of primary mediastinal large B-cell lymphoma in a single institution: the British Columbia experience. *Ann Oncol* 2006;17: 123–130.

Seshadri T, Kuruvilla J, Crump M, Keating A. Salvage therapy for relapsed/refractory diffuse large B cell lymphoma. *Biol Blood Marrow Transplant.* 2008 Mar;14(3):259-67.

Surveillance, Epidemiology, and End Results (SEER) Program Populations (1969-2012) (www.seer.cancer.gov/popdata), National Cancer Institute, DCCPS, Surveillance Research Program, Surveillance Systems Branch, released March 2014.

Sehn LH, Antin JH, Shulman LN et al. Primary diffuse large B-cell lymphoma of the mediastinum: outcome following high-dose chemotherapy and autologous hematopoietic cell transplantation. *Blood* 1998;91: 717–723.

Sehn LH, Donaldson J, Chhanabhai M, et al, Introduction of Combined CHOP Plus Rituximab Therapy Dramatically Improved Outcome of Diffuse Large B-Cell Lymphoma in British Columbia *J Clin Oncol* 2005;23:5027-5033.

Song Y, Chi GYH. A method for testing a prespecified subgroup in clinical trials, Statistics in Medicine, 2007; 26:3535-3549

Wang: Sue-Jane Wang, Approaches to evaluation of treatment effect in randomized clinical trials with genomic subset, Pharmaceutical Statistics, 2007; 6:227-244

Appendices

Appendix A - Revised IWG Response Criteria for Malignant Lymphoma (Cheson 2007).

Complete Remission (CR): CR requires all of the following:

- Complete disappearance of all detectable clinical evidence of disease and disease-related symptoms if present before therapy.
- Typically FDG-avid lymphoma (large cell, mantle cell and follicular lymphomas are all typically FDG-avid): in subjects with no pretreatment PET scan or when the PET scan was positive before therapy, a post-treatment residual mass of any size is permitted as long as it is PET negative.
- Variably FDG-avid lymphomas/FDG avidity unknown: in subjects without a pretreatment PET scan, or if a pretreatment PET scan was negative, all lymph nodes and nodal masses must have regressed to normal size (≤ 1.5 cm in greatest diameter if > 1.5 cm before therapy). Previously involved nodes that were 1.1 to 1.5 cm in their long axis and more than 1 cm in their short axis before treatment must have decreased to ≤ 1.0 cm in their short axis after treatment.
- The spleen and/or liver, if considered to be enlarged before therapy on basis of physical exam or CT scan, must should be normal size on CT scan and not be palpable on physical examination and nodules thought to represent lymphoma must no longer be present.
- A bone marrow aspirate and biopsy is performed only when the patient had bone marrow involvement with lymphoma prior to therapy or if new abnormalities in the peripheral blood counts or blood smear cause clinical suspicion of bone marrow involvement with lymphoma after treatment. The bone marrow aspirate and biopsy must show no evidence of disease by morphology or if indeterminate by morphology it must be negative by immunohistochemistry. The biopsy core sample must be a minimum of 20 mm in length.

Partial Remission (PR): PR requires all of the following:

- ≥ 50% decrease in sum of the product of the diameters (SPD) of up to 6 of the largest dominant nodes or nodal masses. Dominant nodes or nodal masses should be clearly measurable in at least 2 perpendicular dimensions, should be from different regions of the body if possible and should include mediastinal and retroperitoneal nodes if possible.
- No increase in size of nodes, liver or spleen and no new sites of disease.
- If multiple splenic and hepatic nodules are present, they must regress by ≥ 50% in the SPD. There must be a > 50% decrease in the greatest transverse diameter for single nodules.
- Bone marrow is irrelevant for determination of a PR. If patient has persistent bone marrow involvement and otherwise meets criteria for CR the patient will be considered a PR.
- Typically FDG-avid lymphoma: for subjects with no pretreatment PET scan or if the PET scan was positive before therapy, the post-treatment PET scan should be positive in at least one previously involved site. Note: in subjects with follicular lymphoma or mantle-cell lymphoma, a PET scan is only indicated in subjects with one or at most two residual masses that have regressed by 50% on CT scan.

Stable Disease (SD):

- Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD. PET should be positive in typically FDG-avid lymphomas.

Progressive Disease:

Defined by at least one of the following:

- ≥ 50% increase from nadir in the sum of the products of at least two lymph nodes, or if a single node is involved at least a 50% increase in the product of the diameters of this one node.
- Appearance of a new lesion greater than 1.5 cm in any axis even if other lesions are decreasing in size
- Greater than or equal to a 50% increase in size of splenic or hepatic nodules
- At least a 50% increase in the longest diameter of any single previously identified node more than 1 cm in its short axis.
- Lesions should be PET positive in typically FDG-avid lymphomas unless the lesion is too small to be detected by PET (<1.5 cm in its long axis by CT)

Protocol Title:	A Phase 1/2 Multi-Center Study Evaluating the Safety and Efficacy of KTE-C19 in Subjects with Refractory Aggressive Non-Hodgkin Lymphoma (NHL) (ZUMA-1)
Protocol Number:	KTE-C19-101
IND Number:	**016278**
EudraCT Number:	**2015-005007-86**
Clinical Study Sponsor:	Kite Pharma, Inc. 2225 Colorado Avenue Santa Monica, CA 90404 United States of America
Key Sponsor Contacts:	William Go, M.D., Ph.D. Senior Director, Clinical Development Kite Pharma, Inc. 2225 Colorado Avenue Santa Monica, CA 90404 Phone: 424-322-1934 Email: wgo@kitepharma.com Meg Elias, RN BSN Director, Clinical Operations Kite Pharma, Inc. 2225 Colorado Avenue Santa Monica, CA 90404 Phone: 310-742-2803 Email: melias@kitepharma.com Allison Bowen MPM, PMP, BS, BA Chiltern International Inc. 1016 W. Ninth Avenue King of Prussia, PA 19406 Phone: 404.792.7824 Email: Allison.Bowen@Chiltern.com
Version:	**1.0 (Amendment #5)**
Date:	**12 August 2016**

Investigators Agreement

I have read the attached protocol titled: A Phase 1/2 Multi-Center Study Evaluating the Safety and Efficacy of KTE-C19 in Subjects with Refractory Aggressive Non-Hodgkin Lymphoma (NHL) (ZUMA-1) dated **12 August 2016** and agree to abide by all provisions set forth therein.

I agree to comply with the International Conference on Harmonization Tripartite Guideline on Good Clinical Practice and applicable national or regional regulations and guidelines.

I agree and will ensure that financial disclosure statements will be completed by:

- Me (including, if applicable, my spouse, legal partner and dependent children)
- Sub-Investigators (including, if applicable their spouse, legal partner and dependent children)

at the start of the study and for up to one year after the study is completed.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the conduct of the clinical investigation without prior written consent from Kite Pharma Inc.

_____

Signature

_____

Name of investigator

_____

Date

Protocol Synopsis

Title

A Phase 1/2 Multi-Center Study Evaluating the Safety and Efficacy of KTE-C19 in Subjects with Refractory Aggressive Non-Hodgkin Lymphoma (NHL) (ZUMA-1).

Indication

The indication is for the treatment of adult subjects with refractory diffuse large B cell lymphoma (DLBCL), primary mediastinal B cell lymphoma (PMBCL), and transformed follicular lymphoma (TFL).

Study Design

Study KTE-C19-101 is a phase 1/2 multicenter, open-label study evaluating the safety and efficacy of KTE-C19 in subjects with refractory aggressive NHL. The trial will be separated into two distinct phases designated as phase 1 and phase 2.

During phase 1, approximately 6-24 subjects with DLBCL, PMBCL, or TFL will be enrolled to evaluate the safety of KTE-C19 regimens. A safety review team (SRT), internal to the study sponsor, will review the safety data and make recommendations on further study conduct of phase 1 and progression to phase 2 as depicted in Figure 3 and outlined in Section 9.6.

In phase 2**,** approximately **142** subjects will enroll into **3** separate cohorts designated as cohort 1, cohort 2, **and cohort 3.**

- Cohort 1 will enroll approximately 72 adult subjects with refractory DLBCL.
- Cohort 2 will enroll **approximately 20** adult subjects with refractory PMBCL and TFL.
  - TFL is defined as subjects who received prior chemotherapy for follicular lymphoma
- **Cohort 3 will enroll up to 50 adult subjects with refractory or relapsed transplant ineligible DLBCL, PMBCL, or TFL.**

Independent of the phase of the study each subject will follow the same study treatment schedule and procedural requirements. Each subject will proceed through the following study periods:

- Screening period
- Enrollment/Leukapheresis period
- Conditioning chemotherapy period
- Investigational Product (IP) treatment period
- Post treatment assessment period
- Long term follow-up period

For study requirements assigned to each study period, please refer to Section 7 for details.

Study Objectives

The primary objective of phase 1 is to evaluate the safety of KTE-C19 regimens.

The primary objective of phase 2 is to evaluate the efficacy of KTE-C19, as measured by objective response rate in subjects with DLBCL, PMBCL, and TFL. Secondary objectives will include assessing the safety and tolerability of KTE-C19 and additional efficacy endpoints. **Secondary objectives specific to**

cohort 3 are to assess the impact of a prophylactic regimen on the rate of CRS and neurotoxicity and to assess the change in EQ-5D scores from baseline to Month 6.

Hypothesis

Cohort 1 and Cohort 2: This study is designed to differentiate between a treatment that has a true response rate of 20% or less and a treatment with a true response rate of 40% or more. The hypothesis is that the objective response rate to KTE-C19 in **cohorts 1 and 2** is significantly greater than 20%.
Cohort 3: No hypothesis will be tested in cohort 3. Cohort 3 is designed to estimate the response rate in refractory or relapsed DLBCL, PMBCL, and TFL.

Primary Endpoint

- Phase 1: Incidence of adverse events defined as dose-limiting toxicities (DLT)
- Phase 2: Objective response rate (complete response [CR] + partial response [PR]) per the revised International Working Group (IWG) Response Criteria for Malignant Lymphoma (Cheson 2007) as determined by study investigators.

Secondary Endpoint(s) for phase 1 and 2

- Objective response rate per Independent Radiology Review Committee (IRRC) (phase 2 portion)
- Objective response rate (CR + PR) per the revised IWG Response Criteria for Malignant Lymphoma (Cheson 2007) (phase 1 portion)
- Duration of Response
- Progression Free Survival
- Overall Survival
- Incidence of adverse events and clinical significant changes in safety lab values**, including subgroup analyses of subjects in cohort 3 treated prophylactically for safety management**
- Incidence of anti-KTE-C19 antibodies
- Levels of anti-CD19 CAR+ T cells in blood
- Levels of cytokines in serum
- **Changes over time in the EQ-5D scale score and VAS score for subjects assigned to cohort 3**

Exploratory Endpoint(s) for phase 1 and 2

- Objective response rate (CR + PR) per revised IWG Response Criteria for Malignant Lymphoma (Cheson 2007) and duration of second response among subjects retreated with KTE-C19
- Objective response rate and duration of response as determined by IWG Response Criteria for Malignant Lymphoma (Cheson 2014)
- Investigation of potential biomarker development based on assessment of blood cells, tumor cells and the proposed actions of the investigational product

Sample Size

Approximately **148**-**166** subjects

Phase 1: approximately 6-24 subjects
Phase 2: approximately **142** subjects enrolled into **3** cohorts

- Cohort 1: Approximately 72 subjects
- Cohort 2: **Approximately 20** subjects
- **Cohort 3: Up to 50 subjects**

Study Eligibility

Please refer to Section 5 for a complete and detailed list of inclusion and exclusion criteria for both phases of the study.

Treatment

Investigational Product:

- KTE-C19 treatment consists of a single infusion of CAR transduced autologous T cells administered intravenously at a target dose of 2 x 10^6 anti-CD19 CAR+ T cells/kg. Under circumstances where subjects initially respond and subsequently relapse, subjects may be eligible for a second course of conditioning chemotherapy and KTE-C19. Refer to Section 6 for treatment and Section 7.13.8 for retreatment details.

Conditioning Chemotherapy Treatment:

- KTE-C19 is administered after a conditioning chemotherapy regimen consisting of fludarabine 30 mg/m^2/day and cyclophosphamide 500 mg/m^2/day, administered x 3 days. Refer to Section 6 for chemotherapy treatment details.

Additional KTE-C19 regimens may be explored in phase 1 per Section 9.6.

Subjects assigned to cohort 3 will receive the same conditioning chemotherapy and KTE-C19 regimen as described above and will also receive prophylactic tocilizumab and levetiracetam for toxicity management as outlined in Section 6.3.4 and Section 6.4.

Procedures

At specific time points as outlined in the schedule of assessments, subjects will undergo the following **assessments/**procedures: collection of informed consent, general medical history including previous treatments for NHL, physical exam including vital signs and performance status, neurological assessments,blood draws for complete blood count (CBC), chemistry panels, cytokines, C-reactive protein, lymphocyte subsets, anti-KTE-C19 antibodies, replication competent retrovirus (RCR) and anti-CD19 CAR+ T cell analysis. Women of child-bearing potential will undergo a urine or serum pregnancy test.

Subjects will also undergo a baseline electrocardiogram (ECG), echocardiogram (ECHO), brain magnetic resonance image (MRI), a positron emission tomography–computed tomography (PET-CT), **possible bone marrow aspirate/biopsy** and leukapheresis.

Subjects assigned to cohort 3, will complete the EQ-5D questionnaire at baseline and post KTE-C19 (see Section 7.4 and SOA) and will have pre and post KTE-C19 lumbar punctures performed for the collection of CSF (see Section 7.9 and SOA).

Routinely throughout the conduct of the study, subjects will be asked to report concomitant medications and adverse events and will have their disease assessed.

Safety Review Team and Data Safety Monitoring Board

A SRT, that is internal to the study sponsor and in collaboration with at least one study investigator, will review safety data in phase 1 of the study. The SRT will review the safety data and make recommendations on further study conduct of phase 1 and progression to phase 2 as depicted in Figure 3 and outlined in Section 9.6.

An independent Data Safety Monitoring Board (DSMB) will meet when 20 and 50 subjects **in the mITT set of** cohort 1 have had the opportunity to complete their 3 month disease assessment. The DSMB will review safety and efficacy data and be chartered to make trial conduct recommendations based on an analysis of risk vs. benefit. **The DSMB will also meet to review cohort 3 safety data when 20 subjects have been treated with KTE-C19 and have had the opportunity to be followed for 30 days**. The DSMB may meet more often as needed. Refer to Section 9.7 and Section 9.8.

Statistical Considerations

The primary endpoint for the phase 1 portion of the study is the incidence of DLT.

The primary endpoint for the phase 2 portion of the study is objective response rate per the revised IWG Response Criteria for Malignant Lymphoma (Cheson 2007) as determined by the study investigators. This endpoint will be based on a modified intent to treat (mITT) population consisting of all subjects **enrolled and treated with KTE-C19 at a dose of at least 1 X 10^6 anti-CD19 CAR+ T cells/kg.**

This study uses a single-arm design to test for an improvement in response rate in the DLBCL cohort (n=72) and in cohorts 1 and 2 combined (n=**92**). For the test of efficacy this study has ≥90% power to distinguish between an active therapy with a 40% true response rate from a therapy with a response rate of 20% or less with a 1-sided alpha level of 0.025.

The overall 1-sided alpha level of 0.025 will be divided between the inference in cohort 1 and the inference in **cohorts 1 and 2 combined** using the methodology described in Song et al and Wang et al (Song 2007, Wang 2007, Moye 2001). The objective response for cohort 1 will be tested at a 1-sided alpha level of 0.0220 and the objective response rate in **cohort 1 and 2 combined** will be tested at a 1-sided alpha level of 0.0075.

Within cohort 1, 2 interim and 1 primary analyses will be performed.

- Interim analysis 1 will be conducted after 20 subjects in the mITT set have had the opportunity to be evaluated for response 3 months after the KTE-C19 infusion. This interim analysis will be for futility only.
- Interim analysis 2 will be conducted after 50 subjects **in the mITT set** have had the opportunity to be evaluated for response 3 months after the KTE-C19 infusion. This interim analysis will assess early demonstration of efficacy.
- The primary analysis of cohort 1 will occur after **72** subjects in **the mITT set** have had the opportunity to be assessed for response 6 months after the KTE-C19 infusion.

Accrual to the study will continue during interim analysis 1 and interim analysis 2 of cohort 1.

For cohorts 1 and 2 combined, 1 primary analysis will be performed when **72** subjects **in the mITT set in** cohort 1 and **20 subjects in the mITT set in cohort** 2 have had the opportunity to be assessed for response 6 months after the KTE-C19 infusion.

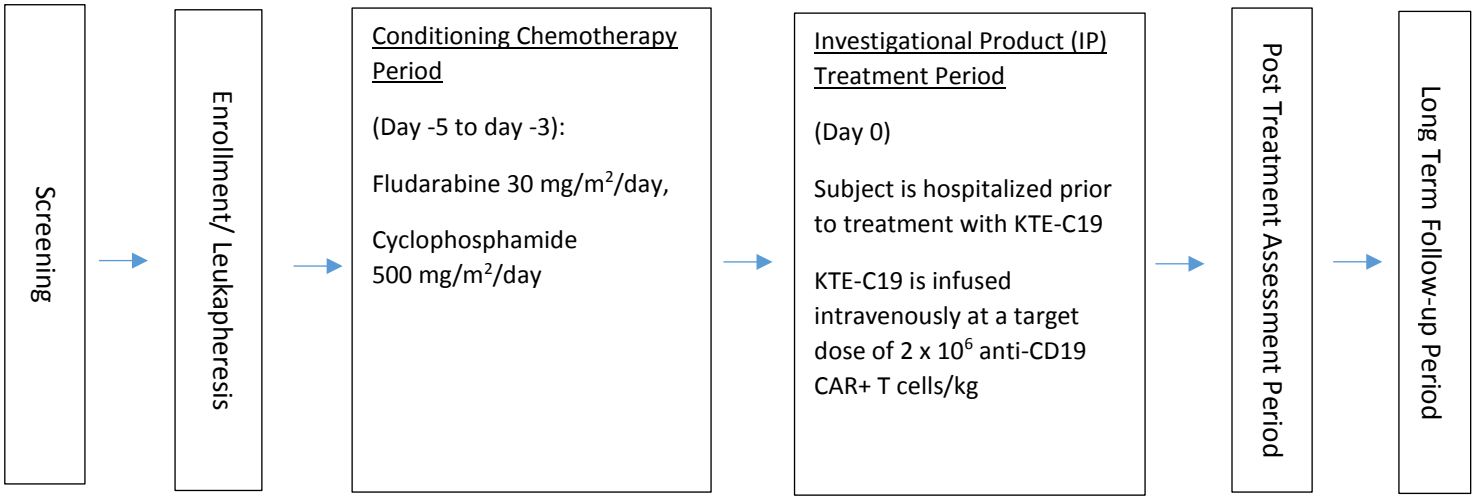
Study Glossary

Abbreviation or Term	Definition/Explanation
AE	adverse event
ALL	acute lymphoblastic leukemia
ANC	absolute neutrophil count
ASCT	autologous stem cell transplant
CAR	chimeric antigen receptor
CAR+	chimeric antigen receptor positive
CBC	complete blood count
CLL	chronic lymphocytic leukemia
CMV	Cytomegalovirus
CNS	central nervous system
CPF	central processing facility
CR	complete response
CRF	case report form
CRS	cytokine release syndrome
CSF	cerebrospinal fluid
CTCAE	common terminology criteria for adverse events
DLBCL	diffuse large B cell lymphoma
DLT	dose-limiting toxicity
DSMB	data safety monitoring board
DVT	deep vein thrombosis
eACT™	engineered autologous cell therapy
EBV	epstein-Barr virus
ECHO	echocardiogram
ECG	electrocardiogram
ECOG	eastern cooperative oncology group
EEG	**electroencephalogram**
End of Study for individual subject	Defined as when the last day that protocol specified assessments are conducted for an individual subject
End of Study (primary completion)	Defined as when the last subject is assessed or received an intervention for the purposes of final collection of data for the primary endpoint at Month 6

Abbreviation or Term	Definition/Explanation
End of Study (end of trial)	Defined as when the last subject is assessed or received an intervention for evaluation in the study, including survival assessments
EQ-5D	**european quality of life-5 dimensions**
FAS	full analysis set
FL	follicular lymphoma
HABA	human anti-bovine antibodies
HAMA	human anti-mouse antibodies
HLH	hemophagocytic lymphohistiocytosis
ICF	informed consent form
ICU	intensive care unit
IP	investigational product
IRB/IEC	institutional review board/independent ethics committee
IRRC	Independent radiological review committee
IWG	International working group
KTE-C19	autologous T cells transduced with retroviral vector containing anti-CD19 CD28/CD3 zeta chimeric antigen receptor
LMWH	low-molecular-weight heparin
LTFU	long term follow-up
LVEF	**left ventricular ejection fraction**
mITT	modified intend to treat
MMSE	mini mental status exam
MRI	magnetic resonance imaging
MSGV1	murine stem cell virus-based vector
NaCl	sodium chloride
NCI	National Cancer Institute
NHL	non-hodgkin lymphoma
OS	overall survival
PET-CT	positron emission tomography–computed tomography
PBMC	peripheral blood mononuclear cells
PMBCL	primary mediastinal B cell lymphoma

Abbreviation or Term	Definition/Explanation
PD	progressive disease
PR	partial response
RCR	replication competent retrovirus
SAE	**serious adverse event**
scFv	single chain variable fragment
SOA	schedule of assessments
SD	stable disease
SRT	safety review team
SUSAR	suspected unexpected serious adverse reactions
Study day 0	Defined as the first day that KTE-C19 is administered to the subject
TEAEs	treatment emergent adverse events
TFL	transformed follicular lymphoma
ULN	upper limit of normal

Study Schema (Phase 1 and Phase 2):



Study KTE-C19-101 is a phase 1-2 single-arm, open-label, multicenter study evaluating the safety and efficacy of KTE-C19 in subjects with refractory DLBCL, PMBCL and TFL.

During phase 1, approximately 6-24 subjects with DLBCL, PMBCL or TFL will be enrolled to evaluate the safety of KTE-C19 regimens. A safety review team (SRT), internal to the study sponsor, will review the safety data and make recommendations on further study conduct of phase 1 and progression to phase 2 as depicted in Figure 3 and outlined in Section 9.6.

Upon SRT recommendation, phase 2 will commence and enroll subjects into **3** separate cohorts designated as cohort 1, cohort 2, **and cohort 3.**

- Cohort 1 will enroll adult subjects with refractory DLBCL.
- Cohort 2 will enroll adult subjects with refractory PMBCL and TFL. Refer to entrance criteria for TFL eligibility requirements.
- **Cohort 3 will enroll adult subjects with refractory or relapsed transplant ineligible DLBCL, PMBCL and TFL**

Independent of the phase of the study each subject will follow the same study treatment schedule and procedural requirements. Each subject will follow through the following study periods: a screening period, an enrollment/leukapheresis period, a conditioning chemotherapy period, an IP treatment period, a post treatment assessment period and a long term follow-up period.

Table of Contents

List of Tables and Figures

1 Objectives

The primary objective of phase 1 is to evaluate the safety of KTE-C19 regimens**.**

The primary objective of phase 2 is to evaluate the efficacy of KTE-C19, as measured by objective response rate in subjects with DLBCL, PMBCL, and TFL. Secondary objectives will include assessing the safety and tolerability of KTE-C19 and additional efficacy endpoints. **Secondary objectives specific to cohort 3 are to assess the impact of a prophylactic regimen on the rate of CRS and neurotoxicity and to assess the change in EQ-5D scores from baseline to Month 6.**

2 Disease Background and Rationale

Non-Hodgkin lymphoma (NHL) is a heterogeneous group of cancers originating in B lymphocytes, T lymphocytes or natural killer cells. In the United States, B cell lymphomas represent 80-85% of cases reported. In 2013, approximately 69,740 new cases of NHL and over 19,000 deaths related to the disease were estimated to occur. Non-Hodgkin lymphoma is the most prevalent hematological malignancy and is the seventh leading site of new cancers among men and women and account for 4% of all new cancer cases and 3% of deaths related to cancer (SEER 2014).

2.1 Diffuse Large B cell Lymphoma

Diffuse large B cell lymphoma (DLBCL) is the most common subtype of NHL, accounting for approximately 30% of NHL cases. There are approximately 22,000 new diagnoses of DLBCL in the United States each year. In the past two decades, progress has been made in understanding the biological heterogeneity of DLBCL and in improving survival with combinations of CHOP and immunotherapy. The addition of ritixumab into combination therapies for DLBCL have greatly improved patient outcomes. However, patients with chemotherapy-refractory DLBCL following treatment under the current standards of care still have a particularly dire prognosis, with no curative treatment options (Flowers 2010).

The population with the highest unmet need continues to consist of patients that do not respond to first line combination chemotherapy (typically R-CHOP) or do not respond to their last course of combination chemotherapy, as the disease is mostly insensitive to subsequent combination chemotherapy (typically R-ICE, R-ESHAP) (Table 1). In a review of 64 patients with DLBCL with disease progression during first line chemotherapy or only transient response (≤90 days) after end of induction treatment, the response rate to second line therapy was 15% and the median overall survival (OS) was 6 months, and no patient survived more than 26 months after first diagnosis (Josting 2000). An analysis of outcome in 1126 patients with DLBCL after first line R-CHOP included 33 patients with primary refractory DLBCL who received second line therapy with curative intent. Only 3 (9%) were able to receive autologous stem cell transplantation (ASCT), and only 1 (3%) patient achieved long term survival (Hitz 2010). Seshadri et al analyzed 120 patients who did not respond to second line platinum-based chemotherapy regimens (e.g., R-ICE) and showed that only 14% responded to their third line therapy (Seshadri 2008). Ardeshna et al followed 19 patients with aggressive NHL, and 9 patients with TFL that did not respond to second line chemotherapy. Only 5 of the 28 total patients (18%) responded to third line chemotherapy (Ardeshna 2005).

Table 1 Historical Responses in Refractory NHL (SD or PD to Last Line of Therapy)

Setting	Outcome to Subsequent Therapy
Refractory to 1st line	
Phillip et al 1995 (n=28)	ORR 21%
Josting et al 2000 (n=64)	ORR 15%, median OS 6 mos
Ardeshna et al 2005 (n=5)	ORR 0%
Hitz et al 2010 (n=33)	Proceeded to ASCT 9%, 3% survived > 1 year
Telio et al 2012 (n = 111)	ORR 23%, median OS 10 mos
Matasar et al 2013 (n=10)	ORR 10%
Refractory to 2nd line	
Moskowitz et al 1999 (n=55)	Median OS 5 mos
Ardeshna et al 2005 (n=28)	ORR 18%, median OS (aggressive NHL) <6 mos
Seshadri et al 2008 (n=73)	ORR 14%
Relapsed post ASCT	
Nagle et al 2013 (N=45)	Median OS 8 mos

These consistently discouraging results demonstrate that new treatment options are urgently needed for patients whose tumors have demonstrated a lack of response to chemotherapy.

This trial will enroll patients with chemo-refractory lymphoma, as evidenced by failure to achieve even a transient or partial response to prior biologic and combination chemotherapy or by early recurrence after ASCT.

2.2 Primary Mediastinal B Cell Lymphoma and Transformed Follicular Lymphoma

Primary mediastinal B cell lymphoma has distinct clinical, pathological, and molecular characteristics compared to DLBCL. Primary mediastinal B cell lymphoma is thought to arise from thymic (medullary) B cells and represents approximately 3% of patients diagnosed with DLBCL. Primary mediastinal B cell lymphoma is typically identified in the younger adult population in the fourth decade of life with a slight female predominance (Sehn 1998, Savage 2006). Gene expression profiling suggests deregulated pathways in PMBCL overlap with Hodgkin lymphoma. Initial therapy of PMBCL generally includes anthracycline-containing regimens with rituximab with or without involved field radiotherapy. A recent phase 2, prospective study of infusional dose-adjusted etoposide, doxorubicin, and cyclophosphamide with vincristine, prednisone, and rituximab (DA-EPOCH-R) demonstrated radiotherapy may not be required (Dunleavy 2013).

Follicular lymphoma (FL), a B cell lymphoma, is the most common indolent (slow-growing) form of NHL, accounting for approximately 20% to 30% of all NHLs. Some patients with FL will transform (TFL) histologically to DLBCL which is more aggressive and associated with a poor outcome. Histological transformation to DLBCL occurs at an annual rate of approximately 3% for 15 years with the risk of transformation continuing to drop in subsequent years. The biologic mechanism of histologic transformation is unknown. Initial treatment of TFL is influenced by prior therapies for follicular lymphoma but generally includes anthracycline-containing regimens with rituximab to eliminate the aggressive component of the disease (NCCN practice guidelines 2014).

Treatment options for relapsed/refractory PMBCL and TFL are similar to those in DLBCL. Given the low prevalence of these diseases, no large prospective randomized studies in these patient populations have

been conducted. Patients with chemotherapy refractory disease have a similar or worse prognosis (Kuruvilla 2008) to those with refractory DLBCL.

In summary, subjects who have refractory, aggressive NHL (e.g., DLBCL, PMBCL, and TFL) have a major unmet medical need and further research with novel treatments are warranted in these populations.

2.3 Study Rationale

As most advanced cancers eventually become refractory to conventional therapies, new treatment modalities are needed. Immunotherapy, which is based on the enhancement of an immune response against the tumor, is a promising approach to treating many cancer types. T cells play an important role in destroying diseased cells throughout the body. Studies with immune checkpoint inhibitors and tumor infiltrating lymphocytes have demonstrated the potential of T cells to treat cancer. T cells need to possess the appropriate specificity for a tumor, be present in sufficient numbers, and overcome any local immunosuppressive factors to be effective. Engineered T cells are a promising approach for cancer therapy (Kershaw 2013).

Engineered Autologous Cell Therapy (eACT™) is a process by which a patient's own T cells are collected and subsequently genetically altered to recognize and target antigens expressed on the cell surface of specific malignancies (Kochenderfer 2013). The ability to genetically engineer human T cells and use them to mediate cancer regression in patients has been demonstrated in a number of studies and has opened possibilities for the treatment of patients with a wide variety of cancer types including B cell malignancies expressing the CD19 antigen.

2.3.1 CD19 and Expression

CD19 is a 95 kD transmembrane protein expressed only in the B cell lineage. It is expressed in all normal B cells starting at the pre-B cell stage until the final differentiation stage and is not expressed in pluripotent hematopoietic stem cells or most plasma cells. The pattern of CD19 expression is maintained in B cell malignancies including all subtypes of B cell NHL, chronic lymphocytic leukemia (CLL), and non-T cell acute lymphoblastic leukemia (ALL) (Blanc 2011) with the exception of multiple myeloma.

2.3.2 Anti-CD19 CAR+ T cell Product

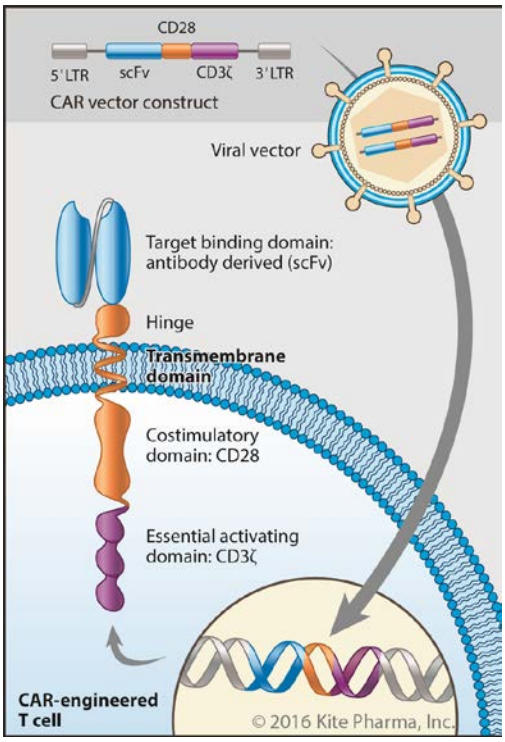
Anti-CD19 chimeric antigen receptor (CAR) positive (+) T cells are autologous human T cells that have been engineered to express an extracellular single chain variable fragment (scFv) with specificity for CD19 linked to an intracellular signaling part comprised of signaling domains from CD28 and CD3ζ (CD3-zeta) molecules arranged in tandem.

An anti-CD19 CAR vector construct has been designed, optimized and initially tested at the Surgery Branch of the National Cancer Institute (NCI, IND 13871) (Figure 1; Kochenderfer 2009, 2010a). The scFv is derived from the variable region of the anti-CD19 monoclonal antibody FMC63 (Nicholson 1997). A portion of the CD28 costimulatory molecule is added, as murine models suggest this is important for the anti-tumor effect and persistence of anti-CD19 CAR+ T cells (Kowolik 2006). The signaling domain of the CD3-zeta chain is essential for T cell activation. These fragments were cloned into the murine stem cell virus-based (MSGV1) vector, utilized to genetically engineer the autologous T cells. Treatment with anti-CD19 CAR+ T cells is currently being administered to subjects with CD19+ B cell malignancies in ongoing NCI protocol (09-C-0082; IND 13871). The same CAR vector construct will be used in this study.

The CAR construct is inserted into the T cells' genome by retroviral vector transduction. Briefly, peripheral blood mononuclear cells (PBMCs) are obtained by leukapheresis and Ficoll separation.

Peripheral blood mononuclear cells are activated by culturing with an anti-CD3 antibody in the presence of recombinant Interleukin 2 (IL-2). Stimulated cells are transduced with a retroviral vector containing an anti-CD19 CAR gene and propagated in culture to generate sufficient engineered T cells for administration.

Figure 1 Anti-CD19 Chimeric Antigen Receptor



2.3.3 Anti-CD19 CAR+ T cell Study Results

Study Design

The NCI study (protocol 09-C-0082; IND 13871) was designed as a phase 1/2, single arm, open label, trial of anti-CD19 CAR+ T cells in subjects with relapsed/refractory B cell malignancies. The primary objective of the study was to determine the safety and feasibility of anti-CD19 CAR+ T cells administered to subjects with B cell malignancies.

Subjects who signed informed consent and met study eligibility were enrolled into the study and underwent leukapheresis to obtain PBMCs for the production of anti-CD19 CAR+ T cells. Subjects were treated with conditioning chemotherapy prior to hospitalization in preparation for a single infusion of anti-CD19 CAR+ T cells on Day 0. Some subjects were then treated with IL-2 (Group 1 only), 3 hours after the anti-CD19 CAR+ T cell infusion. Retreatment of a second dose of anti-CD19 CAR+ T cells was allowed if there was a response that was a partial response (PR) or a complete response (CR) after the first infusion and then subsequent disease progression.

The protocol was originally designed as a dose escalation study, but as a result of dose-limiting toxicities (DLTs), the protocol has been amended several times in an effort to reduce toxicity. As the study proceeded, three groups of subjects have been enrolled:

Group 1 consisted of 8 subjects, including 1 subject who was retreated, dosed with anti-CD19 CAR+ T cells ranging from 3 x 10^6 through 30 x 10^6 anti-CD19 CAR+ T cells/kg. The dose of anti-CD19 CAR+ T cells followed a conditioning regimen consisting of high dose cyclophosphamide (60-120 mg/kg) for 2 days followed by fludarabine (25 mg/m^2) for 5 days. These subjects also received high dose IL-2 (720,000 IU/kg every 8 hours until 15 doses or toxicity precluded additional doses) after the anti-CD19 CAR+ T cell administration to stimulate their proliferation.

Group 2 consisted of 15 subjects, including 2 subjects from Group 1 who were retreated, who received high dose cyclophosphamide and fludarabine and no IL-2 following varying doses of anti-CD19 CAR+ T cell administration (1 x 10^6 through 5 x 10^6 anti-CD19 CAR+ T cells/kg).

Group 3, as of November 30, 2014, has enrolled 11 subjects who have received a reduced conditioning regimen of cyclophosphamide (300 mg/m^2) and fludarabine (30 mg/m^2), both given for 3 concurrent days with no IL-2. The first 7 and last 4 of these subjects received an anti-CD19 CAR+ T cell infusion of 1 x 10^6 anti-CD19 CAR+ T cells and 2 x 10^6 anti-CD19 CAR+ T cells, respectively.

Demographics

As of November 30, 2014, subject demographic and disease characteristics are provided in Table 2. Thirty-two subjects were enrolled, 19 subjects (59%) had DLBCL or PMBCL, 7 subjects (22%) had CLL, and 6 subjects (19%) had other indolent NHL, including indolent follicular lymphoma and splenic marginal zone lymphoma. Most subjects had refractory disease (84%), and had received a median of 3 prior lines of therapy. All subjects with aggressive NHL received prior anti-CD20 therapy, platinum combination chemotherapy, and 95% received prior anthracycline-based chemotherapy (Data on file, Kite Pharma).

Table 2 Demographics

	Group 1 (N = 8)	Group 2 (N = 15)	Group 3 (N = 11)	Total (N = 32)
Age (years)				
Mean (std)	56 (6)	52 (11)	50 (16)	52 (12)
Median	56	55	55	55
Minimum, maximum	47, 63	31, 69	29, 67	29, 69
Gender				
Male	8 (100%)	8 (53%)	11 (100%)	25 (78%)
Female	0 (0%)	7 (47%)	0 (0%)	7 (22%)
Race				
White	8 (100%)	13 (87%)	10 (91%)	29 (91%)
Asian	0 (0%)	1 (7%)	0 (0%)	1 (3%)
Black or African American	0 (0%)	1 (7%)	0 (0%)	1 (3%)
Unknown	0 (0%)	0 (0%)	1 (9%)	1 (3%)
Diagnosis				
CLL	4 (50%)	4 (27%)	0 (0%)	7 (22%)
FL	3 (38%)	0 (0%)	1 (9%)	4 (13%)
SMZL	1 (13%)	1 (7%)	0 (0%)	1 (3%)
iNHL	0 (0%)	1 (7%)	0 (0%)	1 (3%)
DLBCL	0 (0%)	5 (33%)	8 (73%)	13 (41%)
PMBCL	0 (0%)	4 (27%)	2 (18%)	6 (19%)
Prior anti-CD20	7 (88%)	13 (87%)	11 (100%)	30 (94%)
Refractory to last line of therapy (SD/PD to last line)				
Yes	6 (75%)	13 (87%)	9 (82%)	27 (84%)
No	1 (13%)	2 (13%)	0 (0%)	2 (6%)
Unknown	1 (13%)	0 (0%)	2 (18%)	3 (9%)
Lines of prior therapy				
Median (minimum, maximum)	4 (2, 7)	3 (1, 12)	3 (2, 10)	3 (1, 12)

Derived from:
S:\CD19\Clinical Development\data\30NOV2014\TFLs from clinipace\IBTable1.rtf
S:\CD19\Clinical Development\data\30NOV2014\TFLs from clinipace\IBTable1_G1.rtf
S:\CD19\Clinical Development\data\30NOV2014\TFLs from clinipace\IBTable1_G2.rtf
S:\CD19\Clinical Development\data\30NOV2014\TFLs from clinipace\IBTable1_G3.rtf

Pharmacokinetics

The number of anti-CD19 CAR+ T cells in the peripheral blood at various time points after initial administration on Day 0 were evaluated using qPCR analysis and corroborated by standard curves generated by flow cytometry with an antibody reagent specific for scFv present in the anti-CD19 CAR construct (Kochenderfer 2012).

In group 1, 3 x 10^6 to 30 x 10^6 anti-CD19 CAR+ T cells/kg were infused. In the first 6 subjects, the anti-CD19 CAR+ T cells in blood circulation were detected at higher levels within 2 weeks after infusion, reaching up to 0.02-1% of total PBMC, then decayed rapidly and were undetectable after 50 days. Subjects 7 and 8, dosed with the highest number of anti-CD19 CAR+ T cells (28 and 30 x 10^6 anti-CD19 CAR+ T cells/kg, respectively), had higher peak percentages reaching >10% anti-CD19 CAR+ T cells of total PBMC, and longer-term persistence of anti-CD19 CAR+ T cells in blood (>130 and 180 days, respectively).

In group 2, in the absence of interleukin-2 treatment, the anti-CD19 CAR+ T cells showed a similar expansion in the peripheral blood within 2 weeks, followed by decay and complete disappearance from circulation within several weeks (Table 3).

Overall, there was no overt relationship between the dose of anti-CD19 CAR+ T cells and their expansion and persistence in the peripheral blood. Likewise, to date, there was no apparent relationship between the anti-CD19 CAR+ T cell dose, the anti-CD19 CAR+ T cell expansion or persistence in the blood, and the clinical response or the toxicities related to this therapy, respectively.

In groups 1 and 2, there was no secondary expansion of anti-CD19 CAR+ T cells following their primary expansion at 7-14 days post-infusion. There is no evidence of oncogenic transformation ascribable to the genomic insertion of the CAR-expression retrovirus in the subjects tested to date. Group 3 results were not yet available at the time of data cutoff.

Table 3 Anti-CD19 CAR+ T Cell Expansion and Persistence in the Peripheral Blood of Subjects in Group 2

	Total dose of anti-CD19 CAR+ T cells (x 10^6)	**Dose range of anti-CD19 CAR+ T cells/kg in millions (x 10^6)**	**Anti-CD19 CAR+ T cell peak – expressed as number of cells /µL blood**	**Time to peak in days**	**Persistence of anti-CD19 CAR+ T cells in days**
Mean (Range)	210 (105-490)	3.1 (1.2-7.5)	50 (9-777)	10 (7-17)	32 (13-132)

Efficacy

As of November 30, 2014, 32 subjects had been evaluated for safety and 29 subjects had been evaluated for efficacy. The overall response rate for the 29 subjects evaluable for efficacy was 76%. Eleven of 29 subjects (38%) achieved a CR and 11/29 subjects (38%) achieved a PR (Figure 2).

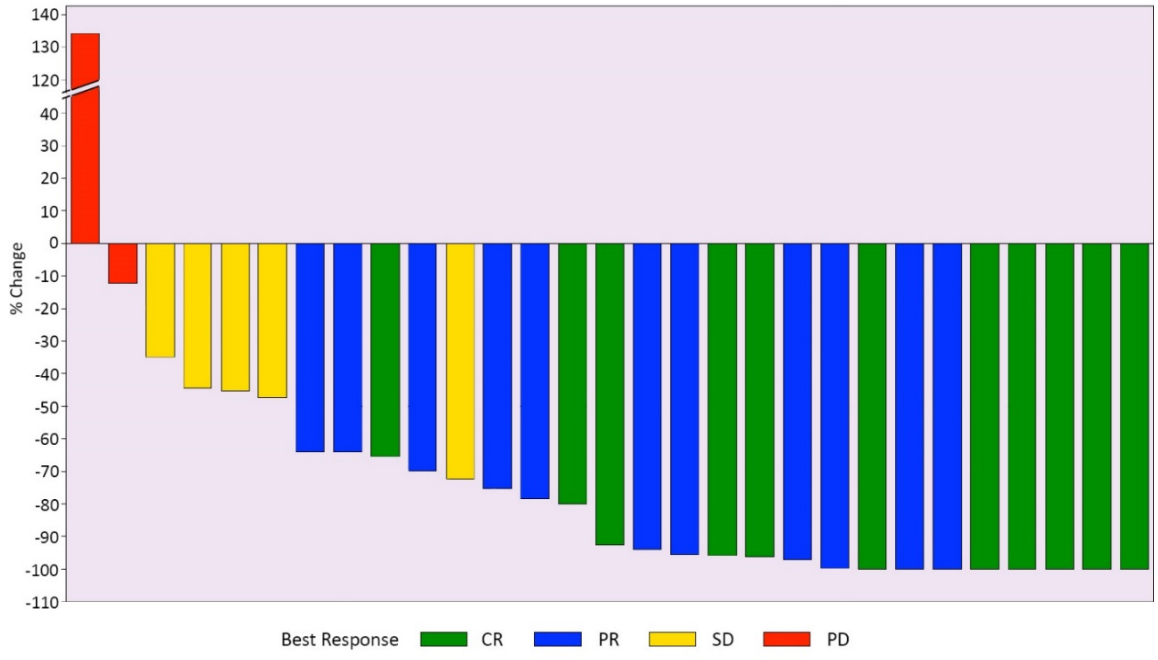
Sixteen of the 29 (55%) evaluable subjects remain in response from their first treatment, with 12 subjects' (including retreated subjects) duration of response exceeding 1 year (Table 4). Three responding subjects were retreated after progression, all have ongoing responses (17.4 to over 52.2 months) (Kochenderfer, 2014).

As indicated in Table 4, 17 of the 19 subjects with refractory aggressive DLBCL/PMBCL were evaluable for disease response (1 subject was not evaluable; 1 subject had not yet been evaluated). Among these 17 subjects, 11 (65%) had a response with 6/17 subjects (35%) achieving a CR. The median duration of response is 7.3 months.

Six of the 7 evaluable subjects (86%) with CLL had a response with 4/7 subjects (57%) achieving a CR. The median duration of response is 22.2 months with 4/7 subjects (57%) still in response including 3 subjects with ongoing responses for greater than 27 months.

Five of the 5 evaluable subjects (100%) with indolent NHL had a response with 1/5 subjects (20%) achieving a CR. The median duration of response is 18.8 months. Five subjects (5/5; 100%) remain in response with 2 subjects responding greater than 45 months.

Figure 2 Best Response to Anti-CD19 CAR+ T Cells in B-Cell Malignancies



Derived from: S:\CD19\Clinical Development\data\30NOV2014\TFLs from clinipace\waterfall.rtf

Table 4 Objective Response Rate and Duration of Response by Tumor Type

Tumor Type (n evaluable)	Overall Response Rate n (%)	Complete Response Rate n (%)	Duration of Response (months) Median (Individual)
Any (n=29)	22 (76%)	11 (38%)	14.9
DLBCL/PMBCL (n=17)	11 (65%)	6 (35%)	7.3 (< 1+, 1.0, 1.2, 5.3+, 6.0, 7.3, 7.9+, 14.1+, 15.7+, 20.3+, 28.5+)
CLL (n=7)	6 (86%)	4 (57%)	22.2 (2.8, 4.6, 17.1+, 27.2+, 31.1+, 35.6+)
Indolent NHL (n=5)	5 (100%)	1 (20%)	18.8 (10.4+, 17.1+, 18.8+, 45.4+, 58.5+)

"+" indicates that the response is still ongoing
Derived from:
S:\CD19\Clinical Development\data\30NOV2014\NCI Data Dec 2014.ppt
S:\CD19\Clinical Development\data\31AUG2014\derived\derived efficacy data 30NOV2014.xls

Safety

Adverse Events

In NCI Protocol (09-C-0082; IND 13871), all Common Terminology Criteria for Adverse Events v3.0 (CTCAE v3.0) grade 3-5 adverse events and grade ≥2 unexpected events were to be reported in the study database. Adverse events that occur after the start of the conditioning regimen are considered treatment-emergent. At the time of the November 30, 2014 data cutoff, 32 subjects had been treated with the anti-CD19 CAR+ T cells with no adverse events yet reported for the last subject treated. Overall safety summaries include all 32 treated subjects. Summaries by group include safety data for subjects 1010003 and 1010004 twice, once when these subjects were treated in Group 1 and second when these subjects were treated in Group 2 (retreatment with anti-CD19 CAR+ T cells).

Summary of Adverse Events

A summary of adverse events is provided in Table 5. Overall, 31 subjects (97%) experienced any adverse event, with 0 subjects (0%) experiencing a worst grade of grade 3, 29 subjects (91%) experiencing a worst grade of grade 4, and 2 subjects (6%) with fatal adverse events. Twenty subjects (63%) experienced an anti-CD19 CAR+ T cell related adverse event; 6 subjects (19%) worst grade of 3, 8 subjects (25%) worst grade 4, and no subjects experienced a grade 5 event. Sixteen subjects (50%) experienced a serious adverse event; 3 subjects (9%) worst grade of 3, 9 subjects (28%) worst grade of 4, and 2 subjects (6%) worst grade of 5.

Table 5 Summary of Adverse Events

	Group 1 (N=8)	Group 2 (N=15)	Group 3 (N = 11)	Overall (N=32)
n (%)				
Any Gr 2-5 AE Gr 3 Gr 4 Gr 5	8 (100) 0 (0) 7 (88%) 1 (13%)	15 (100%) 0 (0%) 14 (93%) 1 (7%)	10 (91%) 0 (0%) 10 (91%) 0 (0%)	31 (97%) 0 (0%) 29 (91%) 2 (6%)
Any Gr 2-5 CAR related Gr 3 Gr 4 Gr 5	3 (37%) 0 (0%) 2 (25%) 0 (0)	11 (73%) 3 (20%) 6 (40%) 0 (0%)	7 (64%) 3 (27%) 0 (0%) 0 (0%)	20 (63%) 6 (19%) 8 (25%) 0 (0%)
Any Serious Gr 3 Gr 4 Gr 5	6 (75%) 2 (25%) 2 (25%) 1 (13%)	8 (53%) 1 (7%) 6 (40%) 1 (7%)	2 (18%) 0 (0%) 1 (9%) 0 (0%)	16 (50%) 3 (9%) 9 (28%) 2 (6%)

Derived from:
S:\CD19\Clinical Development\data\30NOV2014\TFLs from clinipace\IBTable2_G1.rtf
S:\CD19\Clinical Development\data\30NOV 2014\TFLs from clinipace\IBTable2_G2.rtf
S:\CD19\Clinical Development\data\30NOV 2014\TFLs from clinipace\IBTable2_G3.rtf
S:\CD19\Clinical Development\data\30NOV 2014\TFLs from clinipace\IBTable3_G1.rtf
S:\CD19\Clinical Development\data\30NOV 2014\TFLs from clinipace\IBTable3_G2.rtf
S:\CD19\Clinical Development\data\30NOV 2014\TFLs from clinipace\IBTable3_G3.rtf
S:\CD19\Clinical Development\data\30NOV 2014\TFLs from clinipace\TAE_6_13.rtf
S:\CD19\Clinical Development\data\30NOV 2014\TFLs from clinipace\TAE_6_14.rtf
S:\CD19\Clinical Development\data\30NOV 2014\TFLs from clinipace\TAE_6_15.rtf
S:\CD19\Clinical Development\data\30NOV 2014\TFLs from clinipace\TAE_6_16.rtf

Adverse events that occurred in ≥ 10% of subjects are provided in Table 6. Specific adverse events that occurred in ≥ 20% of subjects includes lymphopenia 31 subjects (97%), neutropenia 29 subjects (91%), leukopenia 26 subjects (81%), febrile neutropenia (without documented infection) 21 subjects (66%), thrombocytopenia 20 subjects (63%), anemia 19 subjects (59%), hypotension 11 subjects (34%), infection (documented infection with neutropenia) 9 subjects (28%), fever (without neutropenia) 8 subjects (25%), pain (head/headache) 7 subjects (22%), and hypophosphatemia 7 subjects (22%).

Table 6 Adverse Events ≥ 10% of Subjects

CTC Term	Any Gr 2-5	≥ Grade 3	Grade 3	Grade 4	Grade 5
Subject incidence of adverse events - n (%) (N=32)					
Any Adverse Event	31 (97%)	31 (97%)	0 (0%)	29 (91%)	2 (6%)
Lymphopenia	31 (97%)	31 (97%)	1 (3%)	30 (94%)	0 (0%)
Neutropenia	29 (91%)	29 (91%)	8 (25%)	21 (66%)	0 (0%)
Leukopenia	26 (81%)	26 (81%)	4 (13%)	22 (69%)	0 (0%)
Febrile neutropenia (fever of unknown origin without clinically or microbiologically documented infection)(ANC <1.0 x 10^9/L, fever ≥38.5°C)	21 (66%)	21 (66%)	21 (66%)	0 (0%)	0 (0%)
Thrombocytopenia	20 (63%)	20 (63%)	4 (13%)	16 (50%)	0 (0%)
Anemia	19 (59%)	19 (59%)	19 (59%)	0 (0%)	0 (0%)
Hypotension	11 (34%)	8 (25%)	5 (16%)	3 (9%)	0 (0%)
Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10^9/L)	9 (28%)	9 (28%)	9 (28%)	0 (0%)	0 (0%)
Fever (without neutropenia)	8 (25%)	2 (6%)	2 (6%)	0 (0%)	0 (0%)
Pain (Head/Headache)	7 (22%)	7 (22%)	7 (22%)	0 (0%)	0 (0%)
Hypophosphatemia	7 (22%)	7 (22%)	7 (22%)	0 (0%)	0 (0%)
Creatinine	6 (19%)	6 (19%)	4 (13%)	2 (6%)	0 (0%)
Fatigue	6 (19%)	6 (19%)	6 (19%)	0 (0%)	0 (0%)
Acute vascular leak syndrome	5 (16%)	5 (16%)	4 (13%)	1 (3%)	0 (0%)
Hypocalcemia	5 (16%)	5 (16%)	5 (16%)	0 (0%)	0 (0%)
Hypoxia	5 (16%)	4 (13%)	3 (9%)	1 (3%)	0 (0%)
Infection with normal ANC	5 (16%)	5 (16%)	5 (16%)	0 (0%)	0 (0%)
Aphasia/Dysphasia	5 (16%)	2 (6%)	0 (0%)	2 (6%)	0 (0%)
Hypoalbuminemia	4 (13%)	4 (13%)	4 (13%)	0 (0%)	0 (0%)
Confusion	4 (13%)	3 (9%)	3 (9%)	0 (0%)	0 (0%)
Dyspnea	4 (13%)	3 (9%)	3 (9%)	0 (0%)	0 (0%)
Derived from: S:\CD19\Clinical Development\data\30NOV2014\TFLs from clinipace\IBTable2.rtf					

Adverse Events Attributed to anti-CD19 CAR+ T cells

Adverse events attributed to anti-CD19 CAR+ T cells by the investigator that occurred in ≥ 10% of subjects are provided in Table 7. These events include hypotension 7 subjects (22%), fever without neutropenia 5 subjects (16%), speech impairment 5 subjects (16%), elevated creatinine 4 subjects (13%).

Table 7 Adverse Events Attributed to anti-CD19 CAR+ T Cells

CTC Term	Any Gr 2-5	≥ Grade 3	Grade 3	Grade 4	Grade 5
Subject incidence of adverse events - n (%) (N=32)					
Any Adverse Event	20 (63%)	14 (44%)	6 (19%)	8 (25%)	0 (0%)
Hypotension	7 (22%)	5 (16%)	2 (6%)	3 (9%)	0 (0%)
Fever (without neutropenia)	5 (16%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Speech impairment (e.g., dysphasia or aphasia)	5 (16%)	2 (6%)	0 (0%)	2 (6%)	0 (0%)
Creatinine	4 (13%)	3 (9%)	1 (3%)	2 (6%)	0 (0%)
Any serious Attributed to anti-CD19 CAR+ T cells	9 (28%)	8 (25%)	1 (3%)	7 (22%)	0 (0%)
Derived from: *S:\CD19\Clinical Development\data\30NOV2014\TFLs from clinipace\TAE_6_9.rtf* *S:\CD19\Clinical Development\data\30NOV2014\TFLs from clinipace\TAE_6_21.rtf*					

Dose-Limiting Toxicity

Using the definition of DLT described in the NCI study (09-C-0082; IND 13871), the incidence of DLT within Groups 1, 2 and 3 was 38%, 40%, and 0%, respectively (Data on File, Kite Pharma). With the exception of subject 1010002, DLTs were primarily neurotoxicities, 2 cases of elevated creatinine, and 1 event each of hypoxia and hypotension. Table 8 provides a listing of DLTs. In Group 3 there were no DLTs reported. The conditioning regimen in Group 3 was studied with 2 x 10^6 anti-CD19 CAR+ T cells/kg in the NCI Protocol (09-C-0082; IND 13871).

Table 8 Dose-Limiting Toxicities

Subject No.	Anti-CD19 CAR+ T cells/kg	Dose-Limiting Toxicities (DLT)	Group	Comment
1010002	3 X 10^6	G4 hypoxia G4 influenza infection G5 thrombosis (cerebral thrombi with global infarction)	1	The subject had a culture-proven H1N1 viral pneumonia and died 18 days after his infusion.
1010004	2.5 X 10^6	G4 creatinine	2	Required dialysis
1010007	28 X 10^6	G4 somnolence	1	Required intubation
1010008	30 X 10^6	G4 somnolence	1	Required intubation
1010009	5 X 10^6	G3 confusion/ aphasia G3 cranial nerve VII neuropathy	2	
1010010	4 X 10^6	G3 intermittent confusion/aphasia	2	
1010014	2.5 X 10^6	G3 hypoxia G4 hypotension G3 creatinine G4 somnolence/intermittent confusion	2	Required intubation
1010015	2.5 X 10^6	G4 myoclonus G4 expressive aphasia	2	Required intubation
1010021	1 X 10^6	G4 aphasia G3 motor neuropathy	2	

Group 1: high dose chemotherapy conditioning; IL-2
Group 2: high dose chemotherapy conditioning; no IL-2
Group 3: low dose chemotherapy conditioning; no IL-2

Derived from:
S:\CD19\Clinical Development\data\30NOV2014\TFLs from clinipace\ LAE_1_1.rtf

Cytokine Release Syndrome

Cytokine release is induced by the activated T cells upon engagement with the CD19 target. Using a broad search strategy, treatment-emergent adverse events which may be attributed to CRS include fever, febrile neutropenia, hypotension, acute vascular leak syndrome, elevated creatinine, renal failure, hypoxia, and pleural effusion.

Table 9 provides the incidence of potential CRS adverse events. Twenty-eight (28) (88%) subjects reported adverse events which could be attributed to cytokine release, where 24 subjects (75%) reported a ≥ grade 3 event and 6 subjects (19%) experienced a serious event. Adverse events due to co-therapies such as IL-2 (used in Group 1) and conditioning chemotherapy (causing febrile neutropenia) potentially confound this analysis.

Clinical manifestations of CRS occurred typically in the first week after anti-CD19 CAR+ T cell infusion and were less common in the subjects in Group 3. Only 1 of the 11 subjects in Group 3 experienced grade 3 hypotension, and 4 experienced grade 3 fever. Events of acute vascular leak syndrome, oliguria,

elevated creatinine, and renal failure were reported only in subjects in Groups 1 and 2 (data on file, Kite Pharma).

Table 9 Cytokine Release Syndrome Adverse Events

	Any Gr 2-5 (N = 32)	≥ Grade 3 (N = 32)	Grade 3 (N = 32)	Grade 4 (N = 32)	Grade 5 (N = 32)
Subject incidence of CRS events - n (%)	28 (88%)	24 (75%)	18 (56%)	6 (19%)	0 (0%)
Febrile neutropenia (fever of unknown origin without clinically or microbiologically documented infection)(ANC <1.0 x 10^9/L, fever >=38.5°C)	21 (66%)	21 (66%)	21 (66%)	0 (0%)	0 (0%)
Hypotension	11 (34%)	8 (25%)	5 (16%)	3 (9%)	0 (0%)
Fever (in the absence of neutropenia, where neutropenia is defined as ANC <1.0 x 10^9/L)	8 25%)	2 (6%)	2 (6%)	0 (0%)	0 (0%)
Creatinine	6 (19%)	6 (19%)	4 (13%)	2 (6%)	0 (0%)
Acute vascular leak syndrome	5 (16%)	5 (16%)	4 (13%)	1 (3%)	0 (0%)
Hypoxia	5 (16%)	4 (13%)	3 (9%)	1 (3%)	0 (0%)
Renal failure	2 (6%)	2 (6%)	2 (6%)	0 (0%)	0 (0%)
Pleural effusion (non-malignant)	1 (3%)	1 (3%)	1 (3%)	0 (0%)	0 (0%)
Subject incidence of serious CRS events	6 (19%)	6 (19%)	2 (6%)	4 (13%)	0 (9%)
Derived from: *S:\CD19\Clinical Development\data\30NOV2014\TFLs from clinipace\TAE_7_1.rtf* *S:\CD19\Clinical Development\data\30NOV2014\derived\ CRS_neuro_summary.doc*					

Neurologic Adverse Events

Table 10 provides all neurologic adverse events, predominantly aphasia/dysphasia, confusion, motor neuropathy and somnolence. Thirteen subjects (41%) had severe ≥ grade 3 neurotoxicity, and 11 subjects (34%) experienced a serious event.

The subject who died with a neurotoxicity had an event of CNS cerebrovascular ischemia in the context of viral influenza A infection. This was deemed unrelated to the anti-CD19 CAR+ T cells by the investigator.

Five subjects (16%) with neurotoxicity events required mechanical ventilation for airway protection for neurological adverse events; all of these subjects were in Groups 1 and 2. There have been no subjects intubated in Group 3.

Neurologic adverse events had a median onset of 6 days ranging between days 2 and 17 post anti-CD19 CAR+ T cell infusion, with the exception of grade 4 myelitis which occurred in 1 subject and had an onset at day 110 post anti-CD19 CAR+ T cell infusion. Given the time of onset, presentation and brain MRI findings, this event was considered by the investigator to be related to fludarabine and not attributed to the anti-CD19 CAR+ T cells. The median time to resolution of the neurological adverse event to grade 1 or better was 14 days post infusion.

Table 10 Neurologic Events

CTC Term	Any Gr 2-5 (N = 32)	≥ Grade 3 (N = 32)	Gr 3 (N = 32)	Gr 4 (N = 32)	Gr 5 (N = 32)
Subject incidence of neurologic events - n (%)	18 (56%)	13 (41%)	6 (19%)	7 (22%)	0 (0%)
Speech impairment (e.g., dysphasia or aphasia)	5(16%)	2 (6%)	0 (0%)	2 (6%)	0 (0%)
Confusion	4 (13%)	3 (9%)	3 (9%)	0 (0%)	0 (0%)
Neuropathy: motor	3 (9%)	2 (6%)	2 (6%)	0 (0%)	0 (0%)
Somnolence/depressed level of consciousness	3 (9%)	3 (9%)	0 (0%)	3 (9%)	0 (0%)
Encephalopathy	2 (6%)	2 (6%)	1 (3%)	1 (3%)	0 (0%)
Ataxia (incoordination)	1 (3%)	0 (0%)	(0%)	(0%)	(0%)
CNS cerebrovascular ischemia	1 (3%)	1 (3%)	0 (0%)	1 (3%)	0 (0%)
Dizziness	1 (3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Myelitis	1 (3%)	1 (3%)	0 (0%)	1 (3%)	0 (0%)
Neuropathy: cranial::CN III Pupil, upper eyelid, extra ocular movements	1 (3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Neuropathy: cranial::CN VII Motor-face; Sensory-taste	1 (3%)	1 (3%)	1 (3%)	0 (0%)	0 (0%)
Neuropathy: sensory	1 (3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Pyramidal tract dysfunction (e.g., increased tone, hyperreflexia, positive Babinski, decreased fine motor coordination	1 (3%)	1 (3%)	0 (0%)	1 (3%)	0 (0%)
Seizure	1 (3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Syncope	1 (3%)	1 (3%)	1 (3%)	0 (0%)	0 (0%)
Tremor	1 (3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Subject incidence of serious neurotoxicity events[a]	11 (34%)	9 (28%)	2 (6%)	7 (22%)	0 (0%)
Subject incidence of mechanical ventilation for the management of neurotoxicity	5 (16%)				
Median (range) onset day of neurotoxicity[b] (gr 2-5)	6 (2, 17)				
Median days to resolution to grade 1 or better (from the day of cell dose)	14 (9, 41)				

[a] Two serious events were reported with grade < 3; grade 2 seizure and grade 2 aphasia.
[b] excludes one case of gr 4 myelitis which occurred in 1 subject and had an onset day at 110 days post anti-CD19 CAR + T cell infusion. This event was not attributed to the anti-CD19 CAR + T cells.*Derived from:*
S:\CD19\Clinical Development\data\30NOV2014\TFLs from clinipace\TAE_7_1.rtf
S:\CD19\Clinical Development\data\30NOV2014\derived\ CRS_neuro_summary.doc
Data set aeaeae.xls.

Deaths

Two subjects died within 30 days of the anti CD19 CAR+ T cell infusion. Subject 2, as described above, died 18 days after investigational treatment due to a cerebral infarction concurrent with viral pneumonia, influenza A infection, E coli infection, dyspnea, and hypoxia. Subject 11 had PMBCL, with extensive fibrotic mediastinal lymphoma involvement, died 16 days after investigational treatment. No cause of death determined on autopsy and the autopsy report concluded likely cause of death was cardiac arrhythmia given the mediastinal involvement of PMBCL (Kochenderfer 2014). Neither event was deemed related to anti-CD19 CAR+ T cells by the investigator.

2.3.4 KTE-C19

Kite Pharma is developing an eACT™ (KTE-C19) that targets CD19 expression on B cell malignancies. The CAR vector construct is identical to the one used in NCI protocols (Surgery Branch protocol 09-C-0082; IND 13871; Pediatric Branch protocol 12-C-0112G; IND 14985). Kite Pharma in conjunction with the NCI Surgery Branch has developed a rapid, closed, and bead-less process for the generation of the anti-CD19 CAR+ T cells. Closing the process retains the characteristics of the T cell product (Better 2014). See the investigational product manual for more details.

2.3.5 KTE-C19-101 ZUMA-1 Phase 1 Experience

At the time of the data cut-off date (August 14, 2015), there was a median (min, max) follow up time of 9.5 (4.7, 12.6) weeks after KTE-C19 infusion. There have been 10 subjects screened, 8 enrolled, and 6 enrolled and treated with KTE-C19. The 6 subjects enrolled and treated with KTE-C19 had DLBCL that was either refractory to their last line of treatment or had relapsed within 12 months of autologous stem cell transplant. The median age of the predominantly white cohort of subjects was 63 and the median number of prior therapies was 3, with 3/6 subjects having experienced relapse within 12 months of autologous SCT. Of these 6 subjects, 5 met the criteria for evaluability for the primary endpoint of the phase 1 study, adverse events defined as DLT. The sixth subject received a dose of KTE-C19 below the target dose of 2 x 10^6 anti-CD19 CAR+ T cells/kg, (± 20%) and did not experience a DLT within the 30 day safety window, thus was not evaluable for DLT per protocol. However, since the sixth subject did receive KTE-C19, this subject was included in the safety analysis set, from which the data presented below are drawn. One additional subject was treated following the data cut off to complete enrollment to the DLT-evaluable set. This subject did not have a DLT, SAE, or grade 2 or higher KTE-C19 related AE through the 30 day safety window. Details from this subject are not included below as the subject was treated after the data cut-off.

Treatment-emergent adverse events (TEAEs) are defined as any adverse event that begins on or after the start date of conditioning chemotherapy. In these analyses, adverse event incidences include treatment-emergent adverse events or subsets of treatment-emergent adverse events; adverse events prior to commencement of conditioning chemotherapy and among subjects not treated with KTE-C19 are not included in incidence rates. Adverse events were coded with the Medical Dictionary for Regulatory Activities (MedDRA) version 18.0.

ZUMA-1 Adverse Events

Overall, 6 subjects (100%) experienced any grade 3 or higher TEAE. Three (50%) subjects experienced adverse events of a worst grade of 3, and 2 and 1 (33% and 17%) subjects experienced adverse events of worst grades of 4 and 5, respectively. Six (100%) subjects experienced a KTE-C19-related adverse event, 4 of whom (67%) experienced related adverse events of grade 3 and 1 (17%) experienced a KTE-C19-related grade 4 adverse event. Two (33%) subjects experienced any serious adverse event (SAE), one of

whom experienced a single SAE with a maximum grade of 3 (fatigue) and the other experienced several SAEs, the maximum grade of which was grade 5 (intracranial hemorrhage). One subject (17%) experienced dose-limiting toxicities: CTCAE grade 4 encephalopathy of duration 16 days requiring intubation and Lee grade 4 CRS comprised of acute kidney injury (CTCAE grade 4, duration 11 days), hypotension (CTCAE grade 3, duration 17 days), metabolic acidosis (CTCAE grade 3, duration 16 days), and acute systolic heart failure (CTCAE grade 3, duration 15 days). The most frequent and severe toxicities were related to CRS and neurotoxicity. Four subjects (67%) experienced grade 3 or higher febrile neutropenia and 3 (50%) experienced grade 3 or higher encephalopathy. All grade 3 or higher adverse events are shown in Table 11 and grade 3 and higher laboratory abnormalities, presented as occurring pre- or post-KTE-C19 infusion, are displayed in Table 12. Notably, the single grade 5 event observed in the phase 1 portion of the study was an intracranial hemorrhage that was deemed not related to KTE-C19 cell therapy.

Table 11 ZUMA-1 Incidence of Grade 3 or Higher Adverse Events (Safety Analysis Set, N = 6)

Preferred Term – n (%)	Any	Worst Grade 3	Worst Grade 4	Worst Grade 5
Febrile neutropenia	4 (67)	3 (50)	1 (17)	0 (0)
Encephalopathy	3 (50)	2 (33)	1 (17)	0 (0)
Hypoxia	2 (33)	2 (33)	0 (0)	0 (0)
Neutropenia	2 (33)	0 (0)	2 (33)	0 (0)
Somnolence	2 (33)	2 (33)	0 (0)	0 (0)
Acute kidney injury	1 (17)	0 (0)	1 (17)	0 (0)
Agitation	1 (17)	1 (17)	0 (0)	0 (0)
Anaemia	1 (17)	1 (17)	0 (0)	0 (0)
Ascites	1 (17)	1 (17)	0 (0)	0 (0)
Aspartate aminotransferase increased	1 (17)	1 (17)	0 (0)	0 (0)
Cardiac failure	1 (17)	1 (17)	0 (0)	0 (0)
Delirium	1 (17)	1 (17)	0 (0)	0 (0)
Fatigue	1 (17)	1 (17)	0 (0)	0 (0)
Haemorrhage intracranial	1 (17)	0 (0)	0 (0)	1 (17)
Hypocalcaemia	1 (17)	1 (17)	0 (0)	0 (0)
Hyponatraemia	1 (17)	1 (17)	0 (0)	0 (0)
Hypophosphataemia	1 (17)	1 (17)	0 (0)	0 (0)
Hypotension	1 (17)	1 (17)	0 (0)	0 (0)
Metabolic acidosis	1 (17)	1 (17)	0 (0)	0 (0)
Oral herpes	1 (17)	1 (17)	0 (0)	0 (0)
Pseudomonal sepsis	1 (17)	0 (0)	1 (17)	0 (0)
Pyrexia	1 (17)	1 (17)	0 (0)	0 (0)
Restlessness	1 (17)	1 (17)	0 (0)	0 (0)
Thrombocytopenia	1 (17)	0 (0)	1 (17)	0 (0)
Tremor	1 (17)	1 (17)	0 (0)	0 (0)
Urinary tract infection	1 (17)	1 (17)	0 (0)	0 (0)
Derived from: C:\Users\JJiang\Desktop\Studies\101\SRT1\SRT Data\AE summary tables\3.AE by PT and worst grade tables.sas				

Table 12 ZUMA-1 CTCAE Grade 3 or 4 Laboratory Toxicity Study Day -5 to Study Day 30

	Day – 5 to Day -1 (N=6)			Day 0 to Day 30 (N=6)			Day – 5 to Day 30 (N=6)	
Chemistry – n (%)	Grade 3	Grade 4		Grade 3	Grade 4		Grade 3	Grade 4
Increased Alanine Aminotransferase	0 (0)	1 (17)		0 (0)	0 (0)		0 (0)	1 (17)
Decreased Albumin	0 (0)	0 (0)		1 (17)	0 (0)		1 (17)	0 (0)
Increased Aspartate Aminotransferase	2 (33)	0 (0)		1 (17)	0 (0)		2 (33)	0 (0)
Decreased Calcium	0 (0)	0 (0)		1 (17)	0 (0)		1 (17)	0 (0)
Increased Glucose	1 (17)	0 (0)		0 (0)	0 (0)		1 (17)	0 (0)
Decreased Phosphate	0 (0)	0 (0)		5 (83)	0 (0)		5 (83)	0 (0)
Decreased Potassium	0 (0)	0 (0)		1 (17)	0 (0)		1 (17)	0 (0)
Decreased Sodium	0 (0)	0 (0)		2 (33)	0 (0)		2 (33)	0 (0)
Hematology – n (%)	Grade 3	Grade 4		Grade 3	Grade 4		Grade 3	Grade 4
Decreased ANC	0 (0)	1 (17)		0 (0)	6 (100)		0 (0)	6 (100)
Decreased Platelets	0 (0)	0 (0)		1 (17)	4 (67)		1 (17)	4 (67)
Decreased Hemoglobin	1 (17)	0 (0)		4 (67)	0 (0)		5 (83)	0 (0)
Derived from: *C:\Users\LNavale\Documents\navale\KTE-C19\DLBCL protocol\ongoing data summaries\phase 1\6-subject SRT\Chem30Hyper-Hypo.xls* *C:\Users\LNavale\Documents\navale\KTE-C19\DLBCL protocol\ongoing data summaries\phase 1\6-subject SRT\Heme30.xls*								

ZUMA-1 Serious Adverse Events

Two subjects (33%) experienced SAEs. One subject experienced a treatment emergent serious adverse event of grade 3 fatigue that was deemed not related to KTE-C19. This event met the criteria for a serious adverse event due to a concurrent hospitalization of the patient for suspected disease progression. Four other SAEs occurred in a single subject: grade 4 pseudomonal sepsis and grade 5 intracranial hemorrhage that were deemed not related to KTE-C19 and grade 4 encephalopathy and grade 3 hypotension that were deemed by the investigator to be related to KTE-C19.

ZUMA-1 CRS

In this study, CRS severity is graded according to a modified grading system proposed by Lee (2014), which is summarized in Table 17. Grading is applied on a syndrome level, rather than for individual symptoms. Individual symptoms of CRS are reported as adverse events. For each syndrome reported, investigators are to indicate which specific symptoms (as noted by the AE reporting) are associated with that syndrome. Incidence of CRS is summarized by the subject incidence of the syndrome (as graded by Lee criteria) and includes the subject incidence of the specific symptoms that comprised the CRS graded by CTCAE.

The subject incidence of KTE-C19-related CRS is provided in Table 13. In the safety analysis set, 1 subject (17%) experienced grade 4 CRS. In the safety analysis set, all KTE-C19-related CRS has resolved, with a

median (range) duration of CRS of 6 (1, 17) days. One subject experienced grade 3 or higher CRS; this subject experienced grade 3 and grade 4 CRS of durations 6 and 11 days, respectively.

Table 13 ZUMA-1 Incidence of KTE-C19-Related CRS

	Safety Analysis Set (n=6)		
Event – n (%)	**Any**	**Worst Grade 3**	**Worst Grade 4**
CRS [a] – any	5 (83)	0 (0)	1 (17)
CRS – specific symptoms			
Pyrexia	4 (67)	1 (17)	0 (0)
Hypotension	3 (50)	1 (17)	0 (0)
Acute kidney injury	1 (17)	0 (0)	1 (17)
Cardiac failure	1 (17)	1 (17)	0 (0)
Hypoxia	1 (17)	1 (17)	0 (0)
Metabolic acidosis	1 (17)	1 (17)	0 (0)
Tachycardia	1 (17)	0 (0)	0 (0)

[a] CRS is graded per the revised grading system proposed by Lee et al. This grading system applies to the syndrome; individual symptoms are not graded per Lee et al.

ZUMA-1 Neurotoxicity

Neurotoxicity is identified by use of a search list based on MedDRA version 18.0 preferred terms within the system organ classes of 'Nervous System Disorders' and 'Psychiatric Disorders'.

The subject incidence of KTE-C19-related neurotoxicity is provided in Table 14. In the safety analysis set, 1 subject (17%) experienced grade 4 CRS, 3 subjects (50%) experienced grade 3 neurotoxicity, and 1 subject (17%) experienced grade 4 neurotoxicity. In the safety analysis set, all neurotoxicity related to KTE-C19 has resolved.

Table 14 ZUMA-1 Subject Incidence of KTE-C19-Related Neurotoxicity

	Safety Analysis Set (n=6)		
Event – n (%)	**Any**	**Worst Grade 3**	**Worst Grade 4**
Neurotoxicity[a] – Any	6 (100)	3 (50)	1 (17)
Encephalopathy	5 (83)	2 (33)	1 (17)
Tremor	5 (83)	1 (17)	0 (0)
Somnolence	2 (33)	1 (17)	0 (0)
Agitation	1 (17)	1 (17)	0 (0)
Delirium	1 (17)	1 (17)	0 (0)
Dizziness	1 (17)	0 (0)	0 (0)
Hallucination	1 (17)	0 (0)	0 (0)
Headache	1 (17)	0 (0)	0 (0)
Restlessness	1 (17)	1 (17)	0 (0)
Aphasia	1 (17)	0 (0)	0 (0)
[a] Neurotoxicity is graded per CTCAE 4.03			

All 6 subjects treated in the Phase 1 portion of ZUMA-1 received medications to ameliorate their CRS and/or neurotoxicity events. Four subjects received both tocilizumab and steroids, and 2 received tocilizumab only.

ZUMA-1 Deaths on Study

One subject in the safety analysis set died on study day 16 following KTE-C19 infusion due to an intracranial hemorrhage in the setting of pseudomonas sepsis that was deemed unrelated to KTE-C19 by the site principal investigator. This subject had grade 4 CRS and neurotoxicity as dose-limiting toxicities as described above. Another subject, who never received KTE-C19 and therefore was not included in the safety analysis set, died from rapid disease progression and clinical deterioration after enrollment but prior to leukapheresis.

ZUMA-1 Efficacy

Among the 6 subjects dosed with KTE-C19, 5 were evaluated for response at the time of the data cut-off (median time post infusion: 9.5 weeks) and 1 died prior to the response assessment. Among the 5 subjects assessed for response, 3 experienced a complete response and 1 had a partial response as assessed by PET/CT scan at one month following KTE-C19 therapy. Data collection in this cohort of subjects, including assessment of key secondary endpoints of efficacy including progression free survival and overall survival is ongoing.

The aggregate safety data compiled from the first 5 DLT-evaluable subjects were reviewed by the phase 1 SRT, which consisted of phase 1 principal investigators and Kite Pharma staff on August 18, 2015. The SRT recommended that the conditioning chemotherapy and KTE-C19 treatment regimen was tolerable based on the safety profile in the DLT evaluable subjects. A 6th DLT-evaluable subject was treated after the data cut off. This subject did not have a DLT. One subject had a DLT in the phase 1 as described

above. The SRT met September 22, 2015 to review the phase 1 data form all 6 DLT evaluable subjects. The SRT agreed that, from a safety perspective, this dosing regimen could be taken to phase 2.

See the current version of the investigational brochure for the most recent clinical experience with KTE-C19.

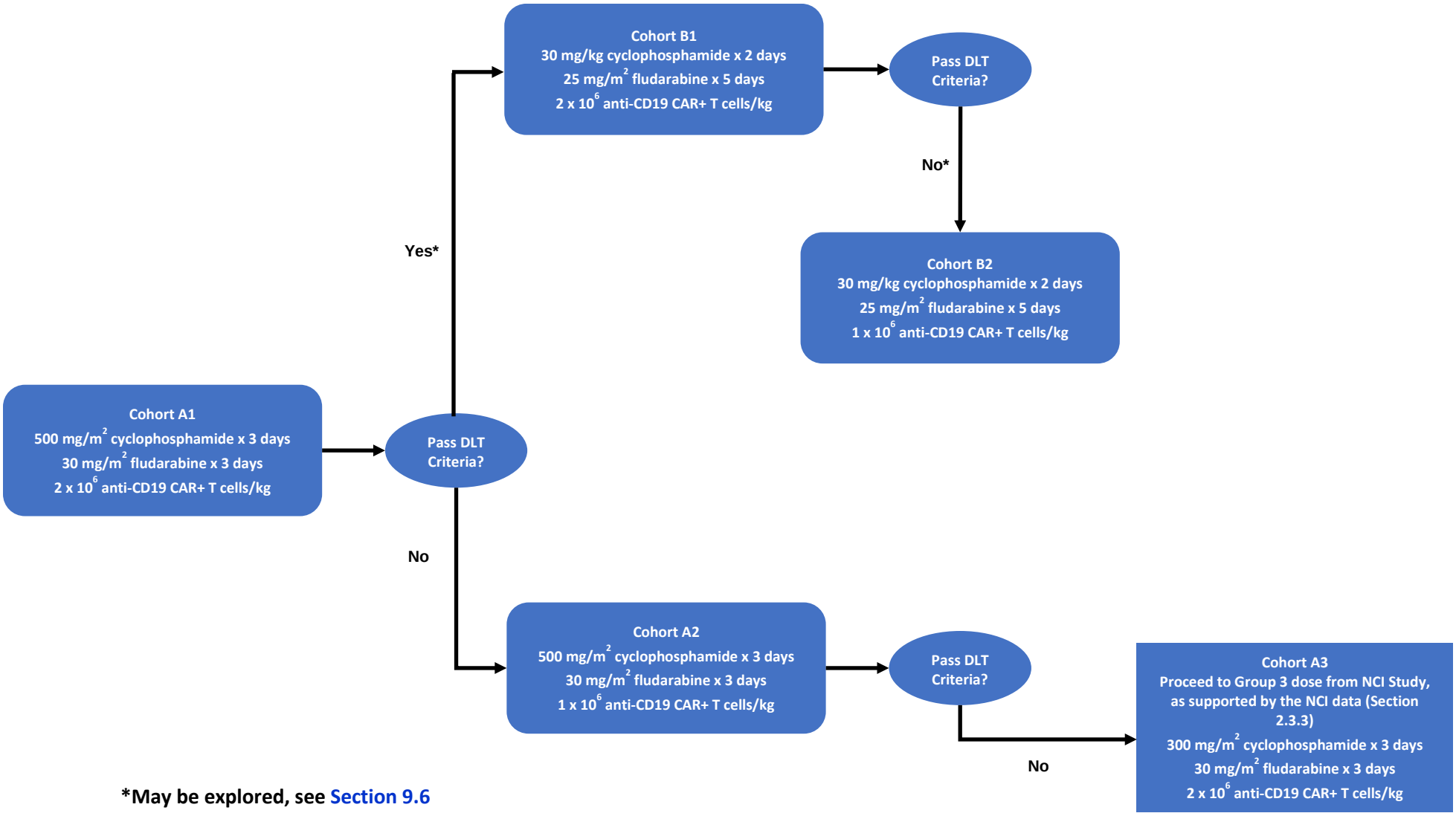
3 Study Design

3.1 General Study Design

Study KTE-C19-101 is a phase 1-2 multicenter, open-label study evaluating the safety and efficacy of KTE-C19 in subjects with refractory NHL. Study KTE-C19-101 will be separated into two distinct phases designated as phase 1 and phase 2.

During phase 1, approximately 6-24 subjects with DLBCL, PMBCL, or TFL will be enrolled to evaluate the safety of KTE-C19 regimens. If the initial regimen is determined to be safe, a higher dose of conditioning chemotherapy may be investigated. If the regimen is determined to not be safe, reduced doses of conditioning chemotherapy and/or KTE-C19 may be explored. A SRT, internal to the study sponsor, will review the safety data and make recommendations on further study conduct of phase 1 and progression to phase 2 as depicted in Figure 3 and outlined in Section 9.6.

Figure 3 Phase 1 Dosing Cohorts and Regimens



***May be explored, see Section 9.6**

In phase 2, subjects will enroll into **3** separate cohorts designated as cohort 1, cohort 2, **and cohort 3.**

- Cohort 1 will enroll adult subjects with refractory DLBCL
- Cohort 2 will enroll adult subjects with refractory PMBCL and TFL
  - TFL is defined as subjects who received prior chemotherapy for follicular lymphoma
- **Cohort 3 will enroll adult subjects with refractory or relapsed transplant ineligible DLBCL, PMBCL, or TFL**

Independent of the phase of the study each subject will follow the same study treatment schedule and procedural requirements. Each subject will proceed through the following study periods:

- Screening period
- Enrollment/Leukapheresis period
- Conditioning chemotherapy period
- Investigational Product (IP) treatment period
- Post treatment assessment period
- Long-term follow-up period

During phase 2 of the study, an independent DSMB will meet when 20 and 50 subjects **in the mITT set** of cohort 1 have had the opportunity to complete the 3 month disease assessment. The DSMB will review safety and efficacy data and be chartered to make trial conduct recommendations based on an analysis of risk vs. benefit. **The DSMB will also meet to review cohort 3 safety data when 20 subjects have been treated with KTE-C19 and have had the opportunity to be followed for 30 days**. The DSMB may meet more often as needed.

For study requirements assigned to each study period, please refer to the schedule of assessments (SOA) and Section 7 for details.

A study schema is drawn out and described at the end of the protocol synopsis section.

3.2 Participating Sites

Approximately **35** centers located in North America **and Europe** will participate in this study. During the conduct of the study, additional regions, countries or sites may be added as necessary.

3.3 Number of Subjects

Participants in this trial will be referred to as “subjects”. It is anticipated that approximately **148-166** subjects will be enrolled into this study as defined below:

Phase 1: approximately 6-24 subjects

Phase 2: approximately **142** subjects enrolled into **3** cohorts

- Cohort 1: Approximately 72 subjects
- Cohort 2: **Approximately 20** subjects
- **Cohort 3: Up to 50 subjects**

It should be noted that Kite Pharma may choose to close enrollment at any time. Please refer to the statistical considerations section of the protocol for sample size estimations.

3.4 Replacement of Subjects

Subjects will continue to be enrolled until the specified number of subjects are attained in the DLT evaluable (phase 1) and mITT sets (phase 2). Subjects who have not received the target dose of KTE-C19 will be retained in the analyses of disposition and safety, where appropriate (Section 10.5).

3.5 Study Duration

3.5.1 Study Duration for Individual Subjects

The duration of the study for individual subjects will vary. For a subject who completes the entire protocol from the date of informed consent through the completion of the long term follow-up period, the duration of the study will take approximately 15 years to complete. However, individual study duration will vary depending on a subject's screening requirements, response to treatment and survival.

The need for prolonged follow-up is based on the potential persistence of gene transfer vectors in treated subjects.

3.5.2 Completion of Study

Completion of the study is defined as the time at which the last subject completes the long term follow-up period visit, is considered lost to follow-up, withdraws consent, or dies. The primary analyses will be conducted when **72** subjects **in the mITT set of** cohort 1 **and 20 subjects in the mITT set of cohort 2** of phase 2 have completed the 6 month disease response assessment, are lost to follow-up, withdraw from the study, or die, whichever occurs first.

4 Subject Screening and Enrollment

All subjects must sign and date the IRB/IEC approved consent form before initiating any study specific procedures or activities that are not part of a subject's routine care. Refer to Section 7 for details.

Each subject who enters the screening period will receive a unique subject identification number before any study specific procedures or activities are initiated. This number will be used to identify the subject throughout the study and must be used on all study documentation related to the subject. Furthermore, the subject identification number must remain constant throughout the entire clinical study, it must not be changed after enrollment or if the subject is rescreened or retreated.

5 Subject Eligibility

5.1 Inclusion Criteria

1. Histologically confirmed aggressive B cell NHL, including the following types defined by WHO 2008:
   - DLBCL not otherwise specified; T cell/histiocyte rich large B cell lymphoma; DLBCL associated with chronic inflammation; Epstein-Barr virus (EBV)+ DLBCL of the elderly; OR
   - primary mediastinal (thymic) large B cell lymphoma
   - transformation of follicular lymphoma to DLBCL will also be included
2. Chemotherapy-refractory disease, defined as one or more of the following:
   - No response to first-line therapy (primary refractory disease); subjects who are intolerant to first-line therapy chemotherapy are excluded
     - PD as best response to first-line therapy
     - SD as best response after at least 4 cycles of first-line therapy (e.g., 4 cycles of R-CHOP) with SD duration no longer than 6 months from last dose of therapy

   OR

- No response to second or greater lines of therapy
  - PD as best response to most recent therapy regimen
  - SD as best response after at least 2 cycles of last line of therapy with SD duration no longer than 6 months from last dose of therapy

  OR
- Refractory post-ASCT
  - Disease progression or relapsed ≤12 months of ASCT (must have biopsy proven recurrence in relapsed subjects)
  - if salvage therapy is given post-ASCT, the subject must have had no response to or relapsed after the last line of therapy

3. Subjects must have received adequate prior therapy including at a minimum:
   - anti-CD20 monoclonal antibody unless investigator determines that tumor is CD20 negative, and
   - an anthracycline containing chemotherapy regimen;
   - for subjects with transformed FL must have received prior chemotherapy for follicular lymphoma and subsequently have chemorefractory disease after transformation to DLBCL
4. At least 1 measurable lesion according to the revised IWG Response Criteria for Malignant Lymphoma (Cheson 2007). Lesions that have been previously irradiated will be considered measurable only if progression has been documented following completion of radiation therapy
5. MRI of the brain showing no evidence of CNS lymphoma
6. At least 2 weeks or 5 half-lives, whichever is shorter, must have elapsed since any prior systemic therapy at the time the subject is planned for leukapheresis, except for systemic inhibitory/stimulatory immune checkpoint therapy. At least 3 half-lives must have elapsed from any prior systemic inhibitory/stimulatory immune checkpoint molecule therapy at the time the subject is planned for leukapheresis (e.g. ipilimumab, nivolumab, pembrolizumab, atezolizumab, OX40 agonists, 4-1BB agonists, etc).
7. Toxicities due to prior therapy must be stable and recovered to ≤ Grade 1 (except for clinically non-significant toxicities such as alopecia)
8. Age 18 or older
9. Eastern cooperative oncology group (ECOG) performance status of 0 or 1
10. ANC ≥1000/uL
11. Platelet count ≥75,000/uL
12. Absolute lymphocyte count ≥100/uL
13. Adequate renal, hepatic, pulmonary and cardiac function defined as:
    - Creatinine clearance (as estimated by Cockcroft Gault) ≥ 60 mL/min
    - Serum ALT/AST ≤2.5 ULN
    - Total bilirubin ≤1.5 mg/dl, except in subjects with Gilbert's syndrome.
    - Cardiac ejection fraction ≥ 50% ,no evidence of pericardial effusion as determined by an ECHO, and no clinically significant ECG findings
    - No clinically significant pleural effusion
    - Baseline oxygen saturation >92% on room air
14. Females of childbearing potential must have a negative serum or urine pregnancy test (females who have undergone surgical sterilization or who have been postmenopausal for at least 2 years are not considered to be of childbearing potential)

Additional criteria specific for Cohort 3:

15. Relapsed transplant ineligible DLBCL, PMBCL, or TFL (must have biopsy proven recurrence in relapsed subjects)

5.2 Exclusion Criteria

201. History of malignancy other than nonmelanoma skin cancer or carcinoma in situ (e.g. cervix, bladder, breast) or follicular lymphoma unless disease free for at least 3 years
202. History of Richter's transformation of CLL
203. Autologous stem cell transplant within 6 weeks of planned KTE-C19 infusion
204. History of allogeneic stem cell transplantation
205. Prior CD19 targeted therapy with the exception of subjects who received KTE-C19 in this study and are eligible for re-treatment
206. Prior chimeric antigen receptor therapy or other genetically modified T cell therapy
207. History of severe, immediate hypersensitivity reaction attributed to aminoglycosides
208. Presence of fungal, bacterial, viral, or other infection that is uncontrolled or requiring IV antimicrobials for management. Simple UTI and uncomplicated bacterial pharyngitis are permitted if responding to active treatment and after consultation with the Kite Medical Monitor.
209. Known history of infection with HIV or hepatitis B (HBsAg positive) or hepatitis C virus (anti-HCV positive). A history of hepatitis B or hepatitis C is permitted if the viral load is undetectable per quantitative PCR and/or nucleic acid testing.
210. Presence of any indwelling line or drain (e.g., percutaneous nephrostomy tube, indwelling foley catheter, biliary drain, or pleural/peritoneal/pericardial catheter). Dedicated central venous access catheters such as a Port-a-Cath or Hickman catheter are permitted
211. Subjects with detectable cerebrospinal fluid malignant cells, or brain metastases, or with a history of CNS lymphoma, cerebrospinal fluid malignant cells or brain metastases
212. History or presence of CNS disorder such as seizure disorder, cerebrovascular ischemia/hemorrhage, dementia, cerebellar disease, or any autoimmune disease with CNS involvement
213. Subjects with cardiac atrial or cardiac ventricular lymphoma involvement
214. History of myocardial infarction, cardiac angioplasty or stenting, unstable angina, or other clinically significant cardiac disease within 12 months of enrollment
215. Requirement for urgent therapy due to tumor mass effects such as bowel obstruction or blood vessel compression
216. Primary immunodeficiency
217. History of deep vein thrombosis or pulmonary embolism within 6 months of enrollment
218. Any medical condition likely to interfere with assessment of safety or efficacy of study treatment
219. History of severe immediate hypersensitivity reaction to any of the agents used in this study
220. Live vaccine ≤ 6 weeks prior to **planned** start of conditioning regimen
221. Women of child-bearing potential who are pregnant or breastfeeding because of the potentially dangerous effects of the preparative chemotherapy on the fetus or infant. Females who have undergone surgical sterilization or who have been postmenopausal for at least 2 years are not considered to be of childbearing potential
222. Subjects of both genders who are not willing to practice birth control from the time of consent through 6 months after the completion of KTE-C19

223. In the investigators judgment, the subject is unlikely to complete all protocol-required study visits or procedures, including follow-up visits, or comply with the study requirements for participation
224. History of autoimmune disease (e.g. Crohns, rheumatoid arthritis, systemic lupus) resulting in end organ injury or requiring systemic immunosuppression/systemic disease modifying agents within the last 2 years

6 Protocol Treatment

6.1 Treatment Terminology

The following terms will be used to describe and define protocol treatment:

- The conditioning chemotherapy regimen used for this study will be fludarabine and cyclophosphamide.
- The investigational product for this study is named KTE-C19.
- The term study treatment refers to all protocol required therapies.

6.2 Study Treatment

6.2.1 Conditioning Chemotherapy

Conditioning chemotherapy will be supplied by the investigative site unless otherwise noted. Refer to the current product label for guidance on packaging, storage, preparation, administration and toxicity management associated with the administration of chemotherapy agents.

6.2.1.1 Fludarabine

Fludarabine phosphate is a synthetic purine nucleoside that differs from physiologic nucleosides in that the sugar moiety is arabinose instead of ribose or deoxyribose. Fludarabine is a purine antagonist antimetabolite.

Refer to the most recent version of the package insert for specific details surrounding the administration of fludarabine.

6.2.1.2 Cyclophosphamide

Cyclophosphamide is a nitrogen mustard-derivative alkylating agent. Following conversion to active metabolites in the liver, cyclophosphamide functions as an alkylating agent; the drug also possesses potent immunosuppressive activity. The serum half-life after IV administration ranges from 3-12 hours; the drug and/or its metabolites can be detected in the serum for up to 72 hours after administration.

Refer to the most recent version of the package insert for specific details surrounding the administration of cyclophosphamide.

6.2.1.3 Mesna

Mesna is a detoxifying agent used to inhibit the hemorrhagic cystitis induced by chemotherapy. The active ingredient mesna is a synthetic sulfhydryl compound designated as sodium-2-mercaptoethane sulfonate with a molecular formula of $C_2H_5NaO_3S_2$.

Mesna should be administered per institutional guidelines. Refer to the most recent version of the package insert for specific details surrounding the administration of mesna.

6.2.2 KTE-C19

This section contains general information and is not intended to provide specific instructions. Refer to the investigational product manual for details and instruction on storage and administration.

KTE-C19 is supplied cryopreserved in cryostorage bags. The product in the bag is slightly cloudy, with cream to yellow color. The cryostorage bags containing KTE-C19 arrive frozen in a liquid nitrogen dry shipper. The bags must be stored in vapor phase of liquid nitrogen and the product remains frozen until the subject is ready for treatment to assure viable live autologous cells are administered to the subject. Several inactive ingredients are added to the product to assure viability and stability of the live cells through the freezing, thawing, and infusion process.

KTE-C19 is a subject-specific product and the intended subject will be identified by a unique subject ID number. Upon receipt, verification that the product and subject-specific labels match the subject's information (e.g., initials, subject ID number) is essential. Do not infuse the product if the information on the subject-specific label does not match the intended subject. The volume of KTE-C19 infused, the thaw start/stop time, and KTE-C19 administration start/stop time, will all be noted in the subject medical record. The product must not be thawed until the subject is ready for the infusion. Refer to the investigational product manual for details and instruction on storage, thawing, and administration of KTE-C19.

To date, subjects have received doses of anti-CD19 CAR+ T cells ranging from 1-30 x 10^6 anti-CD19 CAR+ T cells/kg. There have been no instances of accidental overdose of subjects in this program. In case of accidental overdose, treatment should be supportive. Corticosteroid therapy may be considered if any dose is associated with severe toxicity.

If any problems related to the use of KTE-C19 or any products that support the management of KTE-C19 (e.g., cryostorage bags, subject identification labels) required in this study are identified, please log on to kitepharma.com to report the complaint.

6.2.3 Concomitant Therapy

During the course of the study, investigators may prescribe any concomitant medications or treatment deemed necessary to provide adequate supportive care except those medications listed in Section 6.2.4 Excluded Medications.

All concurrent therapies, including medications, intubation, dialysis, **oxygen,** and blood products, will be recorded from the date of the informed consent through 3 months after completing treatment with KTE-C19. After 3 months of follow-up, only targeted concomitant medication will be collected for **24 months after KTE-C19 infusion or disease progression, whichever occurs first. Targeted concomitant medications include gammaglobulin, immunosuppressive drugs, anti-infective drugs, and vaccinations**.

For subjects who are enrolled but not dosed with KTE-C19, concurrent therapies will only be recorded from the date of the informed consent through 30 days after **the** last **study specific** procedure (e.g., leukapheresis, conditioning chemotherapy). For subjects who are not enrolled (e.g., screen failure or not leukapheresed), only concurrent therapies related to any serious adverse event(s) will be recorded.

Specific concomitant medication collection requirements and instructions are included in the case report form (CRF) completion guidelines.

6.2.4 Excluded Medications

Corticosteroid therapy at a pharmacologic dose (≥5 mg/day of prednisone or equivalent doses of other corticosteroids) and other immunosuppressive drugs must be avoided for 7 days prior to leukapheresis, and 5 days prior to KTE-C19 administration.

Corticosteroids and other immunosuppressive drugs should also be avoided for 3 months after KTE-C19 administration, unless used to manage KTE-C19 related toxicities. Other medications that might interfere with the evaluation of the investigational product, such as non-steroidal anti-inflammatory agents should also be avoided for the same time period unless medically necessary.

Treatment for lymphoma such as chemotherapy, immunotherapy, targeted agents, radiation, and high dose corticosteroid, other than defined/allowed in this protocol, and other investigational agents are prohibited, except as needed for treatment of disease progression after the KTE-C19 infusion.

If permissibility of a specific medication/treatment is in question, please contact the Kite Pharma Medical Monitor.

6.2.5 Subsequent Therapy

Subsequent therapy administered after the KTE-C19 infusion for a subjects' disease such as non-study specified chemotherapy, immunotherapy, targeted agents, as well as stem cell transplant and radiation therapy will be recorded until the subject completes the long term follow up period, is considered lost to follow up, withdraws consent, or dies.

6.3 Study Treatment Schedule

6.3.1 Leukapheresis (Within Approximately 5 Days of Eligibility Confirmation)

Subjects will undergo leukapheresis to obtain leukocytes (white blood cells) for the manufacturing of KTE-C19. Leukapheresed cells obtained at participating centers will be shipped to the Cell Processing Facility (CPF) over night as described in the investigational product manual**.** Once a subject commences leukapheresis, the subject is considered enrolled in the study.

Mononuclear cells will be obtained by leukapheresis (12-15 liter apheresis with a goal to target approximately 5-10 x 10^9 mononuclear cells). The leukapheresed cells are then packaged for expedited shipment to the CPF as described in the investigational product manual.

Upon arrival at the CPF, each subject's leukapheresed product will be processed to enrich for the T cells containing PBMC fraction. T cells are then stimulated to expand and transduced with a retroviral vector to introduce the CAR gene. The T cells are then expanded and cryopreserved to generate the investigational product per CPF SOPs. Once the product has passed certain release tests, it will be shipped back to the treating facility. Following completion of each subjects' conditioning chemotherapy regimen, subjects will receive their respective KTE-C19 infusion.

6.3.2 Study Treatment

Chemotherapy General Instructions

Subjects will receive a non-myeloablative conditioning regimen consisting of cyclophosphamide and fludarabine in order to induce lymphocyte depletion and create an optimal environment for expansion of KTE-C19 *in vivo*. Subjects will initiate conditioning chemotherapy with cyclophosphamide and fludarabine beginning on Day -5 (or Day -7 for cohort B) through Day -1. The 5-day conditioning

chemotherapy regimen may be administered in an outpatient setting. The 7-day conditioning chemotherapy regimen may be administered as an outpatient or inpatient regimen per investigator's discretion.

Subjects should be instructed to drink plenty of liquids during and for 24 hours following the chemotherapy. In general, subjects should be kept well-hydrated but closely monitored to prevent fluid overload.

KTE-C19 General instructions

All subjects will be hospitalized to receive treatment with KTE-C19 followed by an observation period **of at least 7 days**. Subjects will remain in the hospital through Day 7 post treatment with KTE-C19. Subjects should not be discharged from the hospital until all KTE-C19-related non-hematological toxicities return to ≤ grade 1 or baseline. Subjects may be discharged with non-critical and clinically stable or slowly improving toxicities (e.g., renal insufficiency) even if > grade 1, if deemed appropriate by the investigator. Subjects should remain hospitalized for ongoing KTE-C19-related fever, hypotension, hypoxia, or ongoing central neurological toxicity > grade 1, or if deemed necessary by the treating investigator.

6.3.3 Rationale for Study Treatment dosing

Rationale for Conditioning Chemotherapy Dose in Cohort A1

Increasing levels of conditioning chemotherapy correlates with clinical responses to adoptive cell therapy (Dudley 2008). Specifically, there appears to be a link between adequate lymphodepletion and adoptively transferred T cell expansion and function in pre-clinical models. The depth and duration of the lymphodepletion in preclinical models correlate with anti-tumor activity of the adoptively transferred tumor-specific CD8+ T cells (Gattinoni 2005). Lymphodepletion may function by eradicating cytokine sinks for the transferred cells, eliminating T regulatory cells, or enhancing antigen presenting cell activation (Klebanoff 2005). Cyclophosphamide and fludarabine is a potent lymphodepleting regimen. Optimizing the doses of cyclophosphamide and fludarabine to improve the depth and duration of lymphodepletion may enhance the activity of KTE-C19.

As described in Section 2.3.3, the NCI study (09-C-0082; IND 13871) evaluated three groups of subjects based on conditioning regimens. Group 3 evaluated cyclophosphamide (300 mg/m^2) and fludarabine (30 mg/m^2), both given for 3 concurrent days followed by 1-2 x 10^6 anti-CD19 CAR+ T cells. Eleven subjects were treated with this regimen.

The DLT definition in the KTE-C19-101 study was applied to the NCI study (09-C-0082; IND 13871) data in group 3. There were no DLTs (Table 15). The subject incidences of grade 3, 4, 5, and serious adverse events attributed to CAR+ T-cells were 3 (27%), 0 (0%), 0 (0%), and 1 (9%) (Table 5). The objective response rate in this cohort was 60%, including 10% complete responses (Table 15). Many subjects, however, did not achieve blood lymphocyte counts of zero with this conditioning regimen.

To improve the depth and duration of lymphocyte depletion, the conditioning chemotherapy dose in cohort A1 will be cyclophosphamide (500 mg/m^2) and fludarabine (30 mg/m^2) both given for 3 concurrent days with the target dose of 2 x 10^6 anti-CD19 CAR+ T cells/kg. This regimen is currently being evaluated in the NCI study (09-C-0082; IND 13871). Cyclophosphamide (500 mg/m^2) and fludarabine (30 mg/m^2) both given for 3 concurrent days has been studied and tolerated in subjects with B cell malignancies (O'Brien 2001). Similar total doses of cyclophosphamide (900 to 2,000 mg/m^2) and fludarabine (90 to 150 mg/m^2) have been given as a reduced non-myeloblative conditioning regimen in

subjects with B cell malignancies receiving allogeneic stem cell transplants (Khouri 1998). The cyclophosphamide dose used in this regimen (Cohort A1 and currently in the NCI study 09-C-0082; IND 1387) is approximately 38% lower than that used in the Group 2 cyclophosphamide 30 mg/kg conditioning regimen from the NCI study (incidence of DLT 29%, Table 15), with the same lower dose of fludarabine dose as Group 3. Evaluation of higher conditioning chemotherapy doses and/or varying anti-CD19 CAR+ T cell doses would proceed based on the incidence of DLT and evaluation of benefit-risk as described in Section 2.3.3.

Rationale for Conditioning Chemotherapy Dose in Cohort B1

Fifteen subjects were treated in the NCI protocol (09-C-0082; IND 13871) in group 2. Group 2 included subjects with leukemia and lymphoma, 2 different doses of cyclophosphamide (cumulative 60 and 120 mg/kg), and a range of CAR+ T cell doses (1-5 x 10^6/kg). The DLT definition in the KTE-C19-101 study was applied to the NCI study data for subjects in group 2 with B-cell lymphomas, dosed at ≤ 2.5 x 10^6 anti-CD19 CAR+ T cells, and 60 mg/kg cumulative dose of cyclophosphamide to reflect the KTE-C19-101 protocol. Seven subjects met these DLT criteria (Table 15).

The subject incidence of DLT was 29% (Table 15). Subject 1010014, with a best objective response of CR, had specific DLTs of grade 3 renal insufficiency and hypoxia and grade 4 hypotension and somnolence requiring intubation. Subject 1010021, with a best objective response of CR, had a specific DLT of grade 3 motor neuropathy (Table 16). All events were reversible. The subject incidence of grade 3, 4, 5, and serious adverse events attributed to CAR+ T-cells were 1 (14%), 2 (29%), 0 (0%), and 2 (29%). The grade 4 events were grade 4 hypotension, grade 4 somnolence, and grade 4 aphasia/dysphasia (3 events in 2 subjects) (data on file, Kite Pharma). The subject incidence objective response rate in this cohort was 6 (86%), including 5 (71%) complete responses (Table 15) of which 4 are ongoing.

The duration and depth of lymphodepletion appeared to be improved with this higher dose of cyclophosphamide conditioning chemotherapy (data on file). While the sample sizes are small, the data suggest that greater objective and complete response rates may be attained with a higher dose of conditioning chemotherapy regimen (Table 15). Therefore, the regimen in cohort B1 may be explored if the incidence of DLT in cohort A1 is acceptable to further evaluate the impact of conditioning chemotherapy on benefit/risk.

Table 15 Incidence of DLT[a] and Response among Subjects with B-Cell Lymphomas and Dosed with Group 2 and Group 3 Conditioning Chemotherapy and ≤ 2.5 x 10^6 anti-CD19 CAR+ T Cells

Group	N	Incidence of DLT – n(%)	Objective Response Rate - n(%)	Complete Response Rate – n(%)
Group 2 Conditioning (30 mg/kg Cy x 2 days, 25 mg/m^2 Flu x 5 days)	7	2 (29)	6 (86)	5 (71)
Group 3 conditioning (300 mg/m^2 Cy x 3 days, 30 mg/m^2 Flu x 3 days)	10[b]	0 (0)	6 (60)	1 (10)

[a] DLT as determined by the definition proposed in the KTE-C19-101 study
[b] 11 subjects treated in group 3; 10 were followed through day 30 at data cutoff

Table 16 DLT[a] Events Among Subjects with B-Cell Lymphomas and Dosed with ≤ 1-2.0 x 10^6 anti-CD19 CAR+ T Cells and Cyclosphosphamide 30 mg/kg x 2 days-fludarabine 25 mg/m^2 x 5 days

Subject	Event
1010014	Grade 3 renal insufficiency, duration 9 days Grade 4 hypotension, duration 3 days Grade 3 hypoxia, duration 18 days Grade 4 somnolence, duration 10 days, intubation required
1010021	Grade 3 motor neuropathy, duration 18 days
[a] DLT as determined by the definition proposed in the KTE-C19-101 study	

Rationale for Phase 2 Cohort 3

In the multicenter randomized phase 3 CORAL study where subjects were randomized to R-ICE or R-DHAP second-line therapy followed by ASCT with or without rituximab maintenance, 203 subjects across both arms did not proceed with ASCT. These subjects were ineligible for ASCT for multiple reasons including chemorefractory disease, early relapsed disease, residual masses after salvage therapy and intolerance to therapy. The median overall survival of these 203 ASCT ineligible subjects after salvage chemotherapy was only 4.4 months (Van Den Neste 2016). Therefore, the efficacy of KTE-C19 will be estimated in this population which represents a significant unmet need for more effective therapies.

CRS and neurotoxicity are two identified risks associated with KTE-C19. Both CRS and neurotoxicity have led to grade 4 or grade 5 events in the context of anti-CD19 CAR T cells (Schuster 2015, Turtle 2016). The pathophysiology of CRS is well described, but the etiology of the neurotoxicity remains unclear. Currently it is hypothesized that there are two potential mechanisms of the pathophysiology of neurotoxicity: 1) peripheral systemic cytokine release followed by cytokine diffusion across the blood brain barrier (BBB) and/or 2) peripherally activated anti-CD19 CAR T cells translocate across the BBB and elicits a local inflammatory effect. The later hypothesis is supported by emerging evidence of CAR T-cells trafficking to the CSF. To further elucidate the pathophysiology of neurotoxicity, serial CSF collections will be analyzed in this study for cytokines/chemokines/effector molecules and anti-CD19 CAR T cells. In addition, in an attempt to mitigate the onset and severity of CRS and neurotoxicity, prophylactic tocilizumab and levetiracetam will be administered (see Section 6.3.4). It is hypothesized that tocilizumab may lead to fewer activated CAR T-cells trafficking to the CNS and levetiracetum may reduce the risk of clinical or subclinical seizures. Lastly, in an effort to mitigate the severity and/or duration of the neurotoxicity, IT-Ara C with corticosteroids is recommended to be administered at the onset of grade 3 neurotoxicity (see Section 6.4.3).

6.3.4 Study Treatment by Phase

Phase 1:

The study will begin with cohort A1. Subsequent cohorts may be explored as depicted in Figure 3 and outlined in Section 9.6.

Conditioning Chemotherapy

Cohorts A1/A2: Subjects will receive the following 5-day chemotherapy regimen:

- IV hydration with 1L of 0.9% NaCl given prior to cyclophosphamide on the day of infusion followed by:
- Cyclophosphamide 500mg/m^2 IV over 60 minutes on Day -5, Day -4, and Day -3 followed by:
- Fludarabine 30mg/m^2 IV over 30 minutes on Day -5, Day -4, and Day -3 followed by:
- An additional 1L of 0.9% NaCl at the completion of the fludarabine infusion
- Add mesna (sodium 2-mercaptoethanesulfonate) per institutional guidelines

Cohort A3: Subjects will receive the following 5-day chemotherapy regimen:

- The IV hydration is 1L of 0.9% NaCl given prior to cyclophosphamide on the day of infusion followed by:
- Cyclophosphamide 300mg/m^2 IV over 60 minutes on Day -5, Day -4, and Day -3 followed by:
- Fludarabine 30mg/m^2 IV over 30 minutes on Day -5, Day -4, and Day -3 followed by:
- An additional 1L of 0.9% NaCl at the completion of the fludarabine infusion
- Add mesna (sodium 2-mercaptoethanesulfonate) per institutional guidelines

For subjects enrolled into Cohort A1/A2/A3, Day -2 and Day -1 will be rest days before KTE-C19 infusion on Day 0.

Cohorts B1/B2: Subjects will receive the following 7 day chemotherapy regimen:

- IV hydration with 0.9% NaCl. Recommended at 2.6 ml/kg/hr (maximum 200ml/hr) administered as a continuous infusion starting 11 hours pre-cyclophosphamide infusion and continue hydration until 24 hours after last cyclophosphamide infusion:
- Cyclophosphamide 30 mg/kg IV administered on Day -7 an -6 infused over 120 minutes followed by:
- Fludarabine 25 mg/m^2 IV administered on Day -5, Day -4, Day -3, Day -2 and Day -1. Each infusion given over 30 minutes
- Add mesna per institutional guidelines

For subjects enrolled into Cohort B1/B2 there will be no rest days between the last day of chemotherapy (Day -1) and the KTE-C19 infusion on Day 0

KTE-C19:

Cohorts A1/A3/B1: Subjects will receive KTE-C19 treatment consisting of a single infusion of CAR transduced autologous T cells administered intravenously at a target dose of 2 x 10^6 anti-CD19 CAR+ T cells/kg (± 20%; 1.6 x 10^6 anti-CD19 CAR+ T cells/kg to 2.4 x 10^6 anti-CD19 CAR+ T cells/kg). A minimum dose of 1 x 10^6 anti-CD19 CAR+ T cells/kg may be administered. For subjects weighing greater than 100 kg, a maximum flat dose of 2 x 10^8 anti-CD19 CAR+ T cells will be administered.

Cohorts A2/B2: Subjects will receive KTE-C19 treatment consisting of a single infusion of CAR transduced autologous T cells administered intravenously at a target dose of 1 x 10^6 anti-CD19 CAR+ T cells/kg (± 20%; 0.8 x 10^6 anti-CD19 CAR+ T cells/kg to 1.2 x 10^6 anti-CD19 CAR+ T cells/kg). A minimum dose of 0.5 x 10^6 anti-CD19 CAR+ T cells/kg may be administered. For subjects weighing greater than 100 kg, a maximum flat dose of either 1 x 10^8 anti-CD19 CAR+ T cells will be administered.

Phase 2:

Based on the safety profile of the 6 DLT evaluable subjects from the phase 1 portion of the study, the SRT deemed the KTE-C19 dosing regimen explored in cohort A1 to be safe.

In phase 2, subjects will receive the 5-day conditioning chemotherapy regimen used in cohort A1 of the phase 1 portion of the study:

- IV hydration with 1L of 0.9% NaCl given prior to cyclophosphamide on the day of infusion followed by:
- Cyclophosphamide 500mg/m^2 IV over 60 minutes on Day -5, Day -4, and Day -3 followed by:
- Fludarabine 30mg/m^2 IV over 30 minutes on Day -5, Day -4, and Day -3 followed by:
- An additional 1L of 0.9% NaCl at the completion of the fludarabine infusion
- Add mesna (sodium 2-mercaptoethanesulfonate) per institutional guidelines

KTE-C19 will be administered at a target dose of 2 x 10^6 anti-CD19 CAR+ T cells/kg. In addition, subjects who receive doses between 1-2 x 10^6 anti-CD19 CAR+ T cells/kg will be included in the mITT analysis set. For subjects weighing greater than 100 kg, a maximum flat dose of 2 x 10^8 anti-CD19 CAR+ T cells will be administered.

For phase 2 cohort 3, subjects will receive conditioning chemotherapy and KTE-C19 as described above. In addition, subjects will receive levetiracetam (750mg PO or IV BID) starting on Day 0. At the onset of ≥ grade 2 neurotoxicity, levetiracetam should be administered as described in Section 6.4.3 and Table 20. If a subject does not experience any ≥ grade 2 neurotoxicity, levetiracetam should be tapered and discontinued as clinically indicated. Subjects will also receive tocilizumab (8mg/kg IV over 1 hour [not to exceed 800mg]) on Day 2. Further tocilizumab (± corticosteroids) is recommended to be administered at the onset of ≥ grade 2 CRS (see Section 6.4.1 and Table 18) or the onset of ≥ grade 2 neurotoxicity (see Section 6.4.3 and Table 20).

6.4 Toxicity Management

6.4.1 Cytokine Release Syndrome

Cytokine release syndrome (CRS) is a symptom complex associated with the use of monoclonal antibodies and adoptive cell therapies that activate lymphocytes. The condition results from the release of cytokines from cells targeted by antibodies, immune effector cells recruited to the tumor area and subject's immune cells activated during this process. When cytokines are released, a variety of clinical signs and symptoms associated with CRS present themselves including cardiac, gastrointestinal, laboratory (coagulation, renal, and hepatic), respiratory, skin, vascular (hypotension) and constitutional (fever, rigors, headaches, malaise, fatigue, arthralgia, nausea and vomiting).

The goal of CRS management in anti-CD19 CAR+ T cell therapy is to prevent life-threatening conditions while preserving the benefits of antitumor effects. In grading CRS, a CRS severity scale associated with antibody therapeutics was published by NCI investigators. Appreciating the scale needed to be adapted for other therapeutics, to define mild, moderate, severe and life-threatening events, account for overlapping symptoms and guide treatment recommendations, a CRS revised grading system was created by Lee et al. and is highlighted below (Lee 2014). This grading scale outlined in Table 17, and subsequent treatment guidance outlined in Table 18, will be used for study KTE-C19-101.

Table 17 CRS Grading Scale (Excluding Neurologic Toxicity)

Grade	Symptoms
Grade 1	Symptoms are not life threatening and require symptomatic treatment only (e.g., fever, nausea, fatigue, headache, myalgia, malaise)
Grade 2	Symptoms require and respond to moderate intervention Oxygen requirement <40% or hypotension responsive to fluids or low dose of one vasopressor or Grade 2 organ toxicity
Grade 3	Symptoms require and respond to aggressive intervention Oxygen requirement ≥ 40% or hypotension requiring high dose or multiple vasopressors or Grade 3 organ toxicity or Grade 4 transaminitis
Grade 4	Life-threatening symptoms Requirements for ventilator support or Grade 4 organ toxicity (excluding transaminitis)
Grade 5	Death

The following algorithm outlined in Table 18 uses the CRS grading system outlined in Table 17 and is recommended to direct the management of CRS associated with treatment with KTE-C19. This CRS management strategy is based on the experience to date with anti-CD19 CAR+ T cell products (Lee 2014).

Table 18 CRS Treatment Guidance

Cytokine Release Syndrome Grading assessment	Extensive co-morbidities or older age? No/Yes	Treatment
Grade 1: • Fever (defined as ≥ 38.3°C) • Constitutional symptoms	N/A	• Vigilant supportive care • Assess for infection • Treat fever and neutropenia if present, monitor fluid balance, antipyretics, analgesics as needed
Grade 2: • Hypotension: responds to fluids or one low dose vasopressor • Hypoxia: responds to < 40% O^2 • Organ toxicity: grade 2	No	• As above for grade 1 • Monitor organ function closely • **Monitor with continuous cardiac telemetry and pulse oximetry**
Grade 2: • Hypotension: responds to fluids or one low dose vasopressor • Hypoxia: responds to < 40% O^2 • Organ toxicity: grade 2	Yes	• As above for grade 2 • Consider tocilizumab (8mg/kg IV over 1 hr, not to exceed 800mg) ± corticosteroids (e.g., methylprednisolone 1mg/kg BID or dexamethasone 10mg q6hrs)[b]
Grade 3: • Hypotension: requires multiple vasopressors or high dose vasopressors [a] • Hypoxia: requires ≥ 40% O^2 • Organ toxicity: grade 3 **or** grade 4 transaminitis	N/A	
Grade 4 • Mechanical ventilation • Organ toxicity: grade 4 excluding transaminitis	N/A	• As above for grade 2/3 • Corticosteroids (e.g., methylprednisolone 1g/day x3, followed by a rapid taper consisting of 250mg BID x2 days, 125mg BID x2 days and then 60mg BID x2 days) [b]

[a] **Refer to** Table 19.
[b] **Refer to 6.4.1 for recommended doses and details**

There have been reports that some of the severe cytokine release symptoms respond rapidly to infusion of tocilizumab, a monoclonal antibody to the IL-6 receptor in subjects treated with other anti-CD19 CAR+ T cell products (Lee 2014, Davila 2014).

Per Table 18, tocilizumab is recommended to be administered at a dose of 8 mg/kg infused IV over 1 hour (dose should not exceed 800 mg) and repeated every 4-6 hours, as needed based on response, up to 3 doses in a 24hr period. If there is no significant improvement with tocilizumab (e.g. no change in grade of CRS), corticosteroids should be administered (e.g. methylprednisolone 1mg/kg BID or dexamethasone 10mg every 6 hours). High doses of corticosteroids (e.g. methylprednisolone 1g/day x3,

followed by a rapid taper, based on response, consisting of 250mg BID x2 days, then 125mg BID x2 days and then 60mg BID x2 days) should be considered for life-threatening CRS.

Other immunosuppressive agents are also available which target IL-6, TNF-alpha and IL-1, all of which may contribute to CRS pathogenesis. Hence, anti-IL-6 monoclonal antibody (siltuximab), anti-TNF-alpha monoclonal antibody (infliximab), soluble TNF-alpha receptor (etanercept), and IL-1-receptor antagonist (anakinra) could also provide benefit, and have been used to manage CRS (Chen 2016, Lee 2014, Frey 2014). These agents also have efficacy in the setting of macrophage activation syndrome and other syndromes that likely share a common pathophysiology with CRS (Flammiger 2012, Prahalad 2001, Gabay 2010). These agents can be considered in cases that tocilizumab and corticosteroids do not effectively control KTE-C19-related cytokine-mediated toxicity in consultation with the Kite Medical Monitor. Monitoring of C-reactive protein (CRP), LDH, and ferritin may be useful in projecting the course of CRS.

For subjects experiencing severe CRS, consider performing an echocardiogram to assess cardiac function.

Table 19 Vasopressors

Definition of high-dose vasopressors (all doses are required for ≥ 3 hrs):

Vasopressor	Dose
Norepinephrine monotherapy	≥ 20 µg/min
Dopamine monotherapy	≥ 10 µg/kg/min
Phenylephrine monotherapy	≥ 200 µg/min
Epinephrine monotherapy	≥ 10 µg/min
If on vasopressin	Vasopressin + norepinephrine equivalent of ≥ 10 µg/min*
If on combination vasopressors **(not Vasopressin)**	**Norepinephrine** equivalent of ≥ 20 µg/min*

*VASST Trial vasopressor equivalent equation: norepinephrine equivalent dose = [norepinephrine (µg/min)] + [dopamine µg/kg/min) ÷ 2] + [epinephrine (µg/min)] + [phenylephrine (µg/min) ÷ 10]

6.4.1.1 Hypotension and Renal insufficiency

Hypotension and renal insufficiency should be treated as described here or according to medical judgment and institutional practice guidelines. Vigorous intravenous (IV) fluid hydration may be needed to manage hypotension and vascular leak in the setting of CRS. Subjects should be closely monitored to prevent fluid overload, and in some cases continuous veno-venous hemodialysis may be required. Invasive hemodynamic monitoring, for example with a pulmonary artery catheter, may be helpful to optimize fluid management in settings of concurrent severe capillary leak, aggressive IVF administration, and/or pulmonary edema. Anti-hypertensives should be withheld whenever blood pressure begins to decrease below baseline values.

The baseline blood pressure is defined for this guideline as the average of all blood pressure readings obtained during the 24 hours prior to the KTE-C19 infusion. The first treatment for hypotension is administration of IV normal saline boluses.

- Subjects with a systolic blood pressure, diastolic blood pressure, or mean arterial pressure that is 80% or less of their baseline or less than the lower limit of normal should receive 1 Liter normal saline bolus.
- If the hypotension does not respond adequately within one hour, a second bolus at a volume per investigator discretion should be given.

- If hypotension persists despite 2 fluid boluses, consideration should be given for monitoring in the intensive care unit (ICU) and administering vasopressor support.

Note these guidelines may need to be modified based on institutional guidelines and the clinical characteristics of individual subjects, such as pulmonary status, cardiac function, and other factors.

6.4.1.2 Cardiac Toxicity

Cardiac manifestations of CRS may include arrhythmias, decreased ejection fraction/heart failure, myocardial ischemia, and cardiac arrest. Tachycardia is common in the setting of CRS and medications to slow sinus tachycardia should be avoided. Hypotension should be managed as in Section 6.4.1.1. Subjects with persistent hypotension not responsive to fluids should be evaluated for decreased ejection fraction/heart failure by echocardiogram. These toxicities should be emergently managed per medical judgment and institutional practice guidelines.

Subjects with ≥ grade 2 cardiac toxicity should be monitored **with continuous cardiac telemetry and pulse oximetry**. Tocilizumab and corticosteroids should be administered per Section 6.4.1. Follow-up ECGs and echocardiograms are recommended to monitor the course of toxicity to potential resolution.

6.4.2 Hemophagocytic Lymphohistiocytosis

Hemophagocytic lymphohistiocytosis (HLH) is a clinical syndrome that includes overwhelming systemic inflammatory response, cytokine release syndrome (CRS) and multi-organ dysfunction (Jordan 2011, La Rosee 2015). Symptoms include fevers, cytopenias, hepatic dysfunction with hyperbilirubinemia, coagulopathy, tissue hemophagocytosis, with marked elevations in ferritin, CRP, and soluble interleukin-2 receptor (sIL-2R) (Jordan 2011, La Rosee 2015, and Porter 2015). Neurologic findings have also been observed in approximately one-third of cases.

Severe HLH may be triggered by infectious, neoplastic, autoimmune and treatment with immunotherapy (Abe 2002, Ferreria 2006, Lackner 2008, La Rosee 2015). There have been several reports of HLH after treatment with blinatumomab or anti-CD19 CAR T cells (Teachey 2013, Maude 2014, Barrett 2014, Maude 2015, Porter 2015). CRS and HLH may possess similar clinical syndromes with overlapping clinical features and pathophysiology. Cytokine production from activated T-cells may lead to excessive macrophage activation and HLH.

HLH should be considered if there are unexplained elevated liver function tests or cytopenias with or without other evidence of CRS. Monitoring of CRP, ferritin, and soluble IL-2R levels may assist with the diagnosis and define the clinical course. Bone marrow biopsy should be considered to evaluate for hemophagocytosis. Given the overlap with CRS, patients should be managed per CRS Treatment Guidance (Table 18). Suspected cases of HLH should also be discussed with the Kite Medical Monitor.

6.4.3 Neurotoxicity

Neurotoxicity (e.g., encephalopathy, somnolence, aphasia) has been observed with anti-CD19 CAR+ T cell therapies. Evaluation of any new onset ≥ grade 2 neurotoxicity should include a neurological examination (including a MMSE), brain MRI, **electroencephalogram** (EEG), and examination of the cerebrospinal fluid (CSF). **In addition, subjects with ≥ grade 3 neurotoxicity should be monitored with continuous cardiac telemetry and pulse oximetry as clinically indicated.** Endotracheal intubation may be needed for airway protection in severe cases.

Tocilizumab and corticosteroids should be used as per Table 20 to manage neurotoxicity. Tocilizumab at a dose of 8mg/kg **IV over 1 hour (not to exceed 800mg)**and high doses of corticosteroids (e.g. methylprednisolone 1g/day x3, followed by a rapid taper, based on response, consisting of 250mg BID x2 days, 125mg BID x2 days and then 60mg BID x2 days) should be considered for life-threatening neurotoxicity.

For cohort 3, at the onset of ≥ grade 2 neurotoxicity levetiracetam should be increased from a dose of 750mg (PO or IV) BID to a dose of 1000mg (PO or IV) BID. Levetiracetam should be tapered and discontinued as clinically indicated, once neurotoxicity resolves to ≤ grade1 or returns to baseline.

For ≥ grade 3 neurotoxicity, consider intrathecal (IT) cytosine arabinoside (preservative-free Ara-C) at a dose of 100mg with IT corticosteroids (e. g. preservative free dexamethasone 4mg or 100mg hydrocortisone or equivalent).

In some cases multiple anti-epileptic medications may be needed to control seizures. Medications with sedative properties should be avoided if possible unless required to manage seizures.

Leukoencephalopathy has been observed on MRI in the setting of neurotoxicity. Subjects should be managed however based on clinical symptoms. Follow-up MRI is recommended to monitor the course of leukoencephalopathy to potential resolution.

Late onset of neurotoxicity (within approximately a month of discharge from the hospitalization for KTE-C19 infusion) has been observed in some subjects. Patients and their families/caregivers should be warned of the risk at hospital discharge and told to seek immediate medical attention for any new symptoms of neurotoxicity. In addition, patients should be advised not to drive or operate heavy machinery for the first month after discharge and/or until 1 month after complete resolution of neurotoxicity symptoms.

Table 20 Neurotoxicity Management Guidance

Neurotoxicity Grading assessment (CTCAE 4.03)	Treatment	Evaluation
Grade 1: Examples include: • Somnolence-mild drowsiness or sleepiness • Confusion-mild disorientation • Encephalopathy-mild limiting of ADL • Dysphasia-not impairing ability to communicate • Brief partial seizure; no loss of consciousness	• Vigilant supportive care	• Neurological examination • Additional work up as clinically indicated
Grade 2: Examples include: • Somnolence-moderate, limiting instrumental ADL • Confusion-moderate disorientation, limiting instrumental ADL • Encephalopathy-limiting instrumental ADL • Dysphasia-moderate impairing ability to communicate spontaneously • Brief generalized seizure	• Vigilant supportive care • **For cohort 3, increase levetiracetam from a dose of 750mg BID to a dose of 1000mg (PO or IV) BID. Taper and discontinue as clinically indicated, once toxicity resolves to ≤ grade 1 or returns to baseline.** • Consider tocilizumab 8mg/kg IV over 1 hour (not to exceed 800mg)	• Should include brain MRI and evaluation of CSF in addition to neurological exam • Consider EEG as clinically indicated
Grade 3 : Examples include: • Somnolence-obtundation or stupor • Confusion-severe disorientation, limiting self-care ADL • Encephalopathy-limiting self- care ADL • Dysphasia-severe receptive or expressive characteristics, impairing ability to read, write or communicate intelligibly • Multiple seizures despite medical intervention • Weakness limiting self-care ADL; disabling • Complete bowel/bladder incontinence	• **As per above for grade 2** • Repeat tocilizumab, 8mg/kg IV over 1 hour (not to exceed 800mg), q4-6hrs if symptoms have not stabilized or improved within 12-24hrs • Consider corticosteroids (e.g., dexamethasone 10 mg IV q6hrs, methylprednisolone 1mg/kg BID) for worsening symptoms despite tocilizumab • **For cohort 3, consider (IT) cytosine arabinoside (Ara-C) 100mg with IT corticosteroids (e. g., dexamethasone 4mg or hydrocortisone 100mg or equivalent)**	• **As above for grade 2** • **Monitor with continuous cardiac telemetry and pulse oximetry**
Grade 4: • Life-threatening consequences • Urgent Intervention Indicated • Mechanical Ventilation • Life-threatening; prolonged repetitive seizures	• **As per above for grade 2/3** • Corticosteroids (e.g., methylprednisolone 1g/day x3, followed by a rapid taper consisting of 250mg BID x2 days, 125mg BID x2 days and then 60mg BID x2 days)	

Refer to section 6.4.3 for dosing recommendations and details

6.4.4 Fever and Neutropenia

Evaluation for a source of infection should be performed per institutional guidelines. Fevers should be treated with acetaminophen and comfort measures. NSAIDs and corticosteroids should be avoided. Subjects who are neutropenic and febrile should receive broad-spectrum antibiotics. Maintenance IV fluids (normal saline) should be started on most subjects with high fevers, especially if oral intake is poor or if the subject has tachycardia. Filgrastim should be used according to published guidelines (e.g., Infectious Disease Society of America).

6.4.5 Infection Prophylaxis

Subjects should receive prophylaxis for infection with pneumocystis pneumonia, herpes virus, and fungal infections according to NCCN guidelines or standard institutional practice.

6.4.6 B Cell Depletion

It is possible that B cell depletion and hypogammaglobulinemia will occur due to the effects of KTE-C19 on normal B cells. Gammaglobulin will be administered for hypogammaglobulinemia according to institutional guidelines. At a minimum, trough IgG levels should be kept above 400 mg/dL, especially in the setting of infection (ie, Center for International Bone Marrow Transplant Research, American Society for Bone and Morrow Transplantation).

6.4.7 Blood Product Support for Anemia and Thrombocytopenia

All blood products should be irradiated and leukocyte reduced. Using CBCs as a guide, the subject should receive platelets and packed red blood cells as needed. Attempts should be made to keep hemoglobin >8.0 gm/dL and platelets >20,000/mm^3. Provide adequate platelet support prior to performing a lumbar puncture (e.g. platelet >50,000/mm^3). Leukocyte filters should be utilized for all blood and platelet transfusions to decrease sensitization to transfused WBCs and decrease the risk of CMV infection.

6.4.8 Tumor Lysis Syndrome

All subjects with significant malignancy burden and without a contradiction such as allergy should be started on prophylaxis (e.g., allopurinol) as per institutional guidelines prior to initiation of conditioning chemotherapy. Prophylaxis should be discontinued when the risk of tumor lysis has passed.

6.4.9 Deep Vein Thrombosis (DVT) Prophylaxis

DVT prophylaxis should be utilized in all patients with reduced mobility during hospitalization per institutional guidelines. Low molecular weight heparin (LMWH) is encouraged as long as there are no contraindications (e.g. recent surgery, bleeding diathesis, platelet count <50,000/µL) based on benefit/risk. Non-invasive mechanical intermittent pneumatic compression devices for DVT prophylaxis should be used in those who cannot receive anticoagulants due to increased bleeding risk or other concerns (Lyman 2015).

7 Study Procedures

Research staff should refer to the SOAs for an outline of the procedures required. The visit schedule is calculated from KTE-C19 infusion on Day 0.

An overview of study assessments/procedures is outlined below. A description for each period of the study is provided in Section 7.13. Refer to the CRF completion guidelines for data collection requirements and documentation of study procedures.

7.1 Informed Consent

Before a subject's participation in the clinical study, the investigator is responsible for obtaining written informed consent from the subject after adequate explanation of the study design, anticipated benefits and the potential risks. Subjects should sign the most current IRB/IEC approved ICF prior to any study specific activity or procedure is performed.

The consent process and the subject's agreement or refusal to participate in the study is to be documented in the subject's medical records. If the subject agrees to participate, the ICF is to be signed and personally dated by the subject and by the person who conducted the informed consent discussion. The original signed ICF will be retained in accordance with institution policy and IRB/IEC requirements with a copy of the ICF provided to the subject.

All subjects who are enrolled into the study should be re-consented with any updated version of the IRB/IEC approved ICF if relevant to their participation in the study.

7.2 Demographic Data

Demographic data will be collected to include sex, **age**, race, ethnicity**,** and country of enrollment to study their possible association with subject safety and treatment effectiveness.

7.3 Medical and Treatment History

Relevant medical history prior to the start of adverse event reporting will be collected. Relevant medical history is defined as data on the subject's concurrent medical condition that would be typically shared in a referral letter. All findings will be recorded in the CRFs.

In addition to the medical history, all history related to the subject's disease, treatment and response to treatment will be collected and must date back to the original diagnosis.

For subjects who are being referred from another clinic or institution to the participating research center, copies from the subjects chart should be obtained.

7.4 Physical Exam, Vital Signs, Performance Status, and European Quality of Life-5 Dimensions (EQ-5D)

Physical exams will be performed during screening and at times noted in the SOA. Changes noted in subsequent exams when compared to the baseline exam will be reported as an adverse event.

During IP administration/hospitalization, vital signs including blood pressure, heart rate, oxygen saturation, and temperature will be monitored before and after the KTE-C19 infusion and then routinely (every 4-6 hours) while hospitalized. If the subject has a fever (temperature 38.3^{o}C or greater) at any time during hospitalization, vital signs will be monitored more frequently as clinically indicated.

Performance status as measured by the ECOG scale will be performed to quantify the subject's general well-being and ability to perform activities of daily life.

For cohort 3, EQ-5D will be completed by the subject, prior to any other assessment, at the screening visit and at other times noted in the SOA. Subjects who are blind or illiterate may have the EQ-5D questions read to them by the study staff. The study staff, however, cannot interpret any of the questions for the subject. A subject may be exempt from completing the questionnaire if he or she is unable to read the questionnaire in one of the country languages available.

The EQ-5D is a 2 page generic patient questionnaire for assessing the overall health status of a subject. The EQ-5D consists of a 5 dimension descriptive system including questions on mobility, self-care, usual activities, pain/comfort, and anxiety/depression and a visual analogue scale (EQ VAS) which allows the respondent to record health on a vertical scale (e.g., best health to worst health) thus allowing a quantitative measure of health outcome.

7.5 Neurological Assessment

Neurological assessments will be standardized by using the Mini Mental State Examination (MMSE) standard version 2.0. The MMSE is a 5-10 minute, 11-question measure that examines various areas of cognitive function: orientation, attention, immediate recall, short-term recall, language, and the ability to follow simple verbal and written commands.

The mini-mental state examination is divided into two sections. The first part requires vocal responses to the examiner's questions. In the second part of the exam, the subject is asked to follow verbal and written instructions, write a sentence spontaneously, and copy a geometric figure.

A full neurological assessment will be completed during screening to establish a baseline. Subsequent assessments will be performed before KTE-C19 administration on Day 0, on Day 1, and then every other day while hospitalized, as well as at the Week 4 and Month 3 visits. Every attempt should be made to dedicate a single research staff member familiar with or trained in the administration of the MMSE to conduct the assessment to minimize inter-rater variability.

7.6 Cardiac Function

Each subject's cardiac function, as measured by ECHO will be assessed during the screening period to confirm study eligibility. Both LVEF and pericardial effusion will be assessed prior to study entrance by ECHO. An ECHO performed following the subjects last chemotherapy treatment and within 28 days prior to signing the consent may be used for confirmation of eligibility.

To establish a baseline, an ECG will also be performed during the screening period.

7.7 Magnetic Resonance Imaging

Each subject will undergo a screening brain MRI to rule out CNS metastasis during the screening period of the study. **Evaluation of any new onset of ≥ grade 2 neurotoxicity should include a brain MRI as described in Section 6.4.3.**

7.8 Bone Marrow Biopsy

Bone marrow aspirate/biopsy will be performed at screening if not previously performed to assess bone marrow involvement. For subjects with a potential complete response to KTE-C19, a follow-up bone marrow aspirate/biopsy will be performed in subjects presenting with bone marrow involvement prior to therapy or if new abnormalities in the peripheral blood counts or blood smear cause clinical suspicion of bone marrow involvement with lymphoma after treatment. To confirm a complete response, the bone marrow aspirate and biopsy must show no evidence of disease by morphology or if indeterminate by morphology it must be negative by immunohistochemistry. Refer to Section 7.10 and Appendix 1 for treatment response assessment requirements per the revised IWG Response Criteria for Malignant Lymphoma (Cheson 2007). **Bone marrow aspirate/biopsy should also be considered to evaluate HLH as indicated (see Section 6.4.2). A portion of the bone marrow sample collected to evaluate HLH or other toxicities should be submitted to the central laboratory as outlined in the central laboratory manual**.

7.9 Lumbar Puncture

Subjects with symptoms of central nervous system malignancy such as new onset severe headaches, neck stiffness, or any focal neurologic findings on physical exam will have lumbar puncture performed at the screening visit for examination of cerebral spinal fluid. In addition, lumbar puncture may be performed as applicable for subjects with new onset of ≥ grade 2 neurotoxicities post KTE-C19 infusion (see Section 6.4.3).

For subjects who sign the optional portion of the consent form, on study paired lumbar puncture for collection of CSF samples will be performed at baseline prior to KTE-C19 infusion and after KTE-C19 infusion per the schedule of assessments. Samples will be submitted to the central laboratory and analyzed for changes in cytokine levels and presence of CAR T cells.

For subjects assigned to cohort 3, lumbar punctures for the collection of CSF samples will be performed pre and post KTE-C19 infusion at times outlined in the SOA. Samples will be submitted to the central laboratory as outlined in the central laboratory manual. Adequate platelet support should be provided prior to performing a lumbar puncture (e.g. platelet >50,000/mm^3).

7.10 Disease Response Assessment

Subjects will be evaluated for disease response by the site investigator at times indicated in the SOA. Disease assessments will be evaluated per the revised IWG Response Criteria for Malignant Lymphoma (Cheson 2007). Flow cytometric, molecular or cytogenetic studies will not be used to determine response.

Baseline PET-CT scans of the neck, chest, abdomen and pelvis, along with the appropriate imaging of all other sites of disease are required. Subjects will have their first post KTE-C19 infusion planned PET-CT tumor assessment 4 weeks following the KTE-C19 infusion and at regular intervals as highlighted in the SOA during the post treatment and long term follow-up portion of the study.

Post KTE-C19 administration disease assessments will be used to determine the time when progressive disease occurs. Subjects with symptoms suggestive of disease progression should be evaluated for progression at the time symptoms occur even if it is off schedule as per the SOA.

A bone marrow aspirate and biopsy will be performed in subjects who are being assessed for CR. Per the revised IWG Response Criteria for Malignant Lymphoma (Cheson 2007), a bone marrow aspirate and biopsy should be performed only when the subject had bone marrow involvement with lymphoma prior to therapy or if new abnormalities in the peripheral blood counts or blood smear cause clinical suspicion of bone marrow involvement with lymphoma after treatment. The bone marrow aspirate and biopsy must show no evidence of disease by morphology, or if indeterminate by morphology, it must be negative by immunohistochemistry to assign a CR to treatment.

In addition to the investigators assessment, PET-CT scans of all subjects evaluated for disease response for phase 2 will be submitted to and reviewed by an independent central reviewer. For subjects who discontinue the study due to an assessment of progressive disease which was not subsequently confirmed by a central radiology reviewer, any additional imaging data, subsequent to the image in question will be submitted to the central reviewer to confirm disease response.

If the subject is eligible for retreatment with KTE-C19, the last scan prior to retreatment will be considered the baseline for the purpose of evaluating the response to retreatment.

Requirements for PET-CT scans and shipping requirements will be outlined in the study imaging manual.

7.11 Laboratory

The below samples will be collected at the time points indicated in the SOA. Additional samples (e.g., blood, urine, CSF, tissue, etc) may be collected as needed for further safety testing.

Local lab analysis:

- Sodium (Na), Potassium (K), Chloride (Cl), Total CO_2 (bicarbonate), Creatinine, Glucose, Blood Urea nitrogen (BUN), Albumin, Calcium total, Magnesium total (Mg), Inorganic Phosphorus, Alkaline Phosphatase, ALT/GPT, AST/GOT, Total Bilirubin, Direct Bilirubin, LDH, Uric Acid
- C-reactive protein (CRP)
- Complete Blood Count with Differential
- A urine or serum sample will be collected and assessed locally for females of childbearing potential. If the screening pregnancy test is positive, the subjects should not be enrolled. If a standard of care pregnancy test is collected during the course of the study, and the result is positive, the investigator should contact the Kite Pharma Medical Monitor for instructions. If a female partner of a male subject becomes pregnant during the conduct of the study, it must be reported by contacting Kite Pharma Medical Monitor for instructions.

Central lab analysis:

- Blood draws for **PBMC** (lymphocyte subsets, RCR, and anti-CD19 CAR+ T cell) **and cytokine** analysis will be performed at intervals outlined in the SOA.
- Serum samples will also be evaluated for anti-KTE-C19 antibodies or human anti-mouse or anti-bovine antibodies, for analysis at central lab
    - For serum samples that demonstrate increased anti-KTE-C19 human anti-mouse (HAMA) or anti-bovine (HABA) antibodies at the Month 3 visit over baseline values, attempts should be made to obtain and test additional serum samples approximately every 3 months until the antibody levels return to baseline (or becomes negative) or up to 1 year from the completion of treatment, whichever occurs first.
- Archived tumor tissue and, for subjects who sign the optional portion of the informed consent, fresh tumor samples will be collected for central path review and evaluation of prognostic markers specific for NHL and pertaining to the tumor immune environment. Additional analysis may include CD19 expression, gene expression profiling, and analysis of DNA alterations. Remaining tumor samples may be stored for future exploratory analysis of DNA (somatic mutations), RNA, or protein markers.
- **CSF and possibly bone marrow samples will also be collected and analyzed at the central laboratory as outlined in the schedule of assessments and per Section 7.12**
- **See central laboratory manual for details on sample collection, processing, and shipping instructions.**

7.12 Biomarkers

Biomarker analysis will be performed on blood and tumor samples to evaluate predictive and pharmacodynamic markers for KTE-C19. Prognostic markers specific for aggressive NHL and related to the tumor immune environment may also be evaluated in archived and fresh tumor biopsies.

The presence, expansion, persistence, and immunophenotype of transduced anti-CD19 CAR+ T cells will be monitored in the blood primarily by PCR analysis, complemented by flow cytometry. Expansion and persistence in peripheral blood will also be monitored by a CD19 CAR specific quantitative polymerase chain reaction assay (qPCR).

Levels of serum cytokines will also be evaluated in the blood. The following cytokines may be included in the panel: pro-inflammatory and immune modulating cytokines IL-6, TNFα, IL-8, IL-1, IL-2, GM-CSF, IL 15, IL-17a, IFNγ, IL-12p40/p70; immune effector molecules Granzyme A, B, Perforin, sFasL; correlates of acute phase response CRP, SAA and Chemokines MIP-1α, MIP-3α, IP-10, Eotaxin, MCP-4.

Cerebral spinal fluid (CSF), and additional subject samples (e.g., pleural fluid), may be harvested from subjects who develop neurotoxicity or CRS to enable evaluation of inflammatory cytokines and chemokine levels. As applicable, lymphocyte populations residing in the CSF, or other subject samples, may also be monitored for the purpose of understanding the safety profile of KTE-C19.

For subjects who sign the optional portion of the consent form, on study paired lumbar puncture for collection of CSF samples will be performed at baseline prior to KTE-C19 infusion and after KTE-C19 infusion per the schedule of assessments. Samples will be analyzed for changes in cytokine levels and presence of CAR T cells.

For subjects assigned to cohort 3, lumbar punctures for collection of CSF samples will be performed at the following time points: after eligibility is confirmed and prior to start of conditioning chemotherapy, post KTE-C19 infusion on Day 5 (+/- 3 days), and at the Week 4 visit (+/- 3 days). Collection of CSF samples will enable measurement of baseline cytokine levels prior to KTE-C19 infusion. Changes in levels of cytokines post KTE-C19 infusion will be measured at the time of peak CAR T cell expansion (Day 5) and at Week 4 when it is anticipated that cytokine levels would return to baseline levels. Infiltration of CAR T cells will also be assessed by flow cytometry in post KTE-C19 infusion CSF samples. Exploratory analysis of cells, analytes, or immune cell markers within the CSF will be analyzed in conjunction with the clinical data to better understand the pathogenesis of neurotoxicity.

Bone marrow samples may be collected for subjects who develop toxicities post KTE-C19 and will be analyzed centrally by immunohistochemistry for evidence of disease, treatment emergent toxicities (e.g. HLH, pancytopenia) and presence of anti-CD19 CAR T cells.

As KTE-C19 comprises retroviral vector transduced T cells, the presence of replication-competent-retrovirus (RCR) in the blood of treated subjects will be monitored.

In addition, baseline leukapheresis and final KTE-C19 samples will be banked and may be analyzed by immunophenotyping, qPCR, and/or gene expression profiling. Remaining samples may be stored for future exploratory analysis of immune-related DNA, RNA, or protein markers.

Archived tumor tissue will be collected for central path review. Additional analysis may include CD19 expression, gene expression profiling, and analysis of DNA alterations. Remaining tumor samples may be stored for future exploratory analysis of DNA, RNA, or protein markers.

For subjects who sign the optional portion of the consent form (and for all subjects with accessible tumor), on-study paired core biopsies of tumor will be performed, at baseline and after KTE-C19 infusion when we expect expansion and tumor infiltration with CAR T cells. In addition, persisting, relapsing or emerging lesions could also be biopsied to help determine eligibility for re-treatment or mechanisms of

tumor resistance. Exploratory analysis of tumor or immune cell markers that correlate with response to KTE-C19 or disease prognosis will be analyzed.

The above samples and any other components from these samples may be stored up to 15 years to address exploratory research scientific questions related to the treatment or disease under study. Each subject will have the right to have the sample material destroyed at any time by contacting the investigator who in turn can contact the sponsor. The investigator should provide the sponsor the study and subject number so that the sample can be located and destroyed.

For subjects who withdraw consent, any samples that were not requested to be returned or destroyed will remain with the sponsor and any data that may be generated will be entered in the study database.

7.13 Description of Study Periods

Investigative sites will maintain a log of all screened subjects who were reviewed and evaluated for study participation. Information collected on the screening log should include limited information such as the date of screening, date the subject was enrolled or the reason for why the subject failed screening.

7.13.1 Screening

The screening period begins on the date the subject signs the IRB/IEC approved ICF and continues through confirmation of enrollment. Informed consent must be obtained before completion of any non-standard of care study specific procedures. Procedures that are part of standard of care are not considered study specific procedures and may be performed prior to obtaining consent and used to confirm eligibility. Confirmation of this data must occur within the time allowance as outlined below and in the SOA.

After written informed consent has been obtained, subjects will be screened to confirm study eligibility and participation. Only subjects who meet the eligibility criteria listed in Section 5 and who commence leukapheresis will be enrolled in the study. If at any time prior to enrollment the subject fails to meet the eligibility criteria, the subject should be designated as a screen failure on the subject screening log with the reasons for failing screening.

The following assessments/procedures are to be completed during the screening period at the time points outlined in the SOA:

- Medical history and disease assessment
- Physical examination including height and weight
    - Subjects with symptoms of central nervous system malignancy such as new onset severe headaches, neck stiffness, or any focal neurologic findings on physical exam will have lumbar puncture for examination of cerebral spinal fluid.
- Vital signs ,including blood pressure, heart rate, oxygen saturation, and temperature
- ECOG performance status
- **For subjects assigned to cohort 3, EQ-5D questionnaire (prior to any other assessments/procedures being performed)**
- Neurological assessment including MMSE
- ECG
- ECHO for LVEF and pericardial effusion assessment
    - An ECHO performed following the subjects last chemotherapy treatment and within 28 days prior to signing the consent may be used for confirmation of eligibility

- Imaging Studies
  - Brain MRI
  - Baseline PET CT of the neck, chest, abdomen and pelvis
    - PET-CT performed following the subjects last line of therapy and prior to signing the consent may be used for confirmation of eligibility**.**
    - If PET CT is performed > 28 days prior to the initiation of conditioning chemotherapy or if subject receives any anti-cancer therapy between screening and conditioning chemotherapy, the scans must be repeated to establish a new baseline. PET CT should be performed as close to enrollment as possible.
- **Bone marrow aspirate/biopsy as needed (if not done at initial diagnosis or between diagnosis and screening)**
- Labs
  - Chemistry panel
  - CBC with differential
  - β-HCG pregnancy test (serum or urine) on all women of child-bearing potential
- Serious Adverse Event reporting (refer to Section 9 for safety reporting guidelines)
- Concomitant medications documentation and previous cancer treatment history
- Once eligibility confirmed, collection of archived tumor sample, as well as fresh tumor sample**(s)** and CSF samples (for subjects who signed the optional portion of the consent)
- **For subjects assigned to cohort 3, lumbar puncture for collection of CSF samples to be performed after eligibility confirmed and prior to start of conditioning chemotherapy**

7.13.2 Rescreening

Subjects who fail to meet the eligibility criteria will be allowed to rescreen one time. Subjects will perform the assessment that initially resulted in the subject failing screening including any other procedures that fell outside of the designated screening window (i.e., lab assessments or PET-CT scans).

7.13.3 Enrollment/Leukapheresis

Subjects must have no evidence of a clinically significant infection prior to leukapheresis. Should a subject have a clinically significant infection immediately prior to leukapheresis, cell collection must be delayed until the event resolves. If leukapheresis is delayed beyond 5 days, baseline CBC with differential and chemistry panel must be repeated to confirm eligibility.

Corticosteroid therapy at a pharmacologic dose (≥5 mg/day of prednisone or equivalent doses of other corticosteroids) and other immunosuppressive drugs must be avoided for 7 days prior to leukapheresis.

Once a subject commences leukapheresis, the subject will be considered enrolled into the study.

The following procedures/requirements will occur on the leukapheresis collection day and as outlined in the SOA:

- Vital signs, including blood pressure, heart rate, oxygen saturation, and temperature
- Weight
- Labs (to be drawn prior to leukapheresis, on the day of or day before leukapheresis)
  - Chemistry panel
  - CBC with differential
  - C-reactive protein (CRP); if CRP is ≥ 100 mg/dL a call must be made to the Kite Medical Monitor before proceeding with conditioning chemotherapy

  - Anti-CD19 CAR+ T cells
  - Lymphocyte subsets
  - Cytokine levels
  - Anti-KTE-C19 antibodies
- Leukapheresis
- Adverse/Serious Adverse Event reporting
- Concomitant medications documentation

7.13.4 Conditioning Chemotherapy Period

If any screening assessments or procedures are repeated between screening and the start of conditioning chemotherapy and results are outside the eligibility criteria (Section 5), please contact the Kite Medical Monitor before proceeding with conditioning chemotherapy.

Subjects must have no evidence of clinically significant infection, no clinically significant cardiac dysfunction, serum creatinine <2 x ULN, and no acute neurological toxicity >grade 1 (with the exception of peripheral sensory neuropathy) prior to conditioning chemotherapy. Should an event exceed these criteria immediately prior to conditioning chemotherapy, conditioning chemotherapy must be delayed until the event resolves. In addition, if the C-reactive protein (CRP) collected on the day of leukapheresis is >100 mg/dL or if the temperature is ≥38.0 C within 48 hours prior to conditioning chemotherapy, please contact the Kite Medical Monitor before proceeding with the conditioning chemotherapy.

The following procedures will be completed during Day -5 (or Day -7 in Cohort B) to Day -1 at the time points outlined in the SOA:

- Vital signs, including blood pressure, heart rate, oxygen saturation, and temperature
- Labs (to be drawn prior to chemotherapy)
  - Chemistry Panel
  - CBC with differential
- Fludarabine and cyclophosphamide administration
- Adverse/Serious Adverse Event reporting
- Concomitant medications documentation

7.13.5 Investigational Product Treatment Period

Subjects will be hospitalized to receive treatment with KTE-C19 followed by a **minimum 7 day** observation period.

Subjects must have no evidence of clinically significant infection, no clinically significant cardiac dysfunction, serum creatinine <2 x ULN, and no acute neurological toxicity > grade 1 (with the exception of peripheral sensory neuropathy) prior to KTE-C19 infusion. Furthermore, subjects must not be receiving systemic anti-microbials for the treatment of an active infection within 48 hours before KTE-C19 administration (prophylactic use of anti-microbials are allowed). **Corticosteroid therapy at a pharmacologic dose (≥5 mg/day of prednisone or equivalent doses of other corticosteroids) and other immunosuppressive drugs must be avoided for 5 days prior to KTE-C19 administration**.

Should an event not meet these criteria immediately prior to receiving KTE-C19, the KTE-C19 infusion must be delayed until the event resolves. If the KTE-C19 infusion is delayed >2 weeks, conditioning chemotherapy must be repeated**, unless otherwise agreed between the investigator and the Kite Medical Monitor**. In all cases of KTE-C19 infusion delays, contact the Kite Medical Monitor for guidance.

In addition to the above criteria, if the subjects' temperature is ≥ 38.0 C within 48 hours prior to KTE-C19 infusion, a call must be made to the Kite Medical Monitor before proceeding with the KTE-C19 infusion.

Subjects will remain in the hospital through Day 7 post treatment with KTE-C19. Subjects should not be discharged from the hospital until all KTE-C19-related non-hematological toxicities return to ≤ grade 1 or return to baseline. Subjects may be discharged with non-critical and clinically stable or slowly improving toxicities (e.g., renal insufficiency) even if >grade 1, if deemed appropriate by the investigator. Subjects should remain hospitalized for ongoing KTE-C19-related fever, hypotension, hypoxia, or ongoing central neurological toxicity >grade 1, or if deemed necessary by the treating investigator.

Given the possibility that a subject could develop CRS or neurotoxicity after discharge from the hospital, subjects and their family members/caregivers should be educated on potential symptoms such as fever, dyspnea, confusion, aphasia, dysphasia, somnolence, encephalopathy, ataxia, or tremor. If subjects develop these symptoms, they should be instructed to immediately contact the principal investigator or seek immediate medical attention.

During this period, the following procedures will be completed at the time points outlined in the SOA:

- **Neurological assessment including** MMSE
  - MMSE will be administered before treatment with KTE-C19 on Day 0, then on Day 1 and every other day through hospitalization
- Vital signs including blood pressure, heart rate, oxygen saturation, and temperature, every 4-6 hours during hospitalization
- Labs (before KTE-C19 infusion, as described in the SOA)
  - Chemistry Panel
  - CBC with differential
  - Lymphocyte subsets
  - Cytokine levels
  - Anti-CD19 CAR+ T cells
  - RCR analysis
- Infusion of KTE-C19
- **For subjects assigned to cohort 3, administer tocilizumab at a dose of 8mg/kg IV over 1 hour (not to exceed 800mg) on Day 2. See Section 6.4.1 and Section 6.4.3 for further details on additional tocilizumab administration for toxicity management.**
- **For subjects assigned to cohort 3, administer levetiracetam at a dose of 750mg (PO or IV) BID starting on Day 0. See Section 6.4.3 for further details on administration and discontinuation of levetiracetam for toxicity management. If subject does not experience any neurotoxicity ≥ grade 2, taper and discontinue levetiracetam as clinically indicated.**
- **For subjects assigned to cohort 3, lumbar puncture for collection of CSF samples at Day 5 (+/- 3 days)**
- As applicable, lumbar puncture, for subjects with new onset grade ≥ 2 neurologic symptoms after KTE-C19 infusion or subjects who signed the optional portion of the consent, should be completed for examination of CSF.
- Collection of fresh tumor sample(s) for subjects who signed the optional portion of the consent (anytime between Day 7 and Day 14) Adverse/Serious Adverse Event reporting (refer to Section 9 for safety reporting guidelines)
- Concomitant medications documentation

Monitoring of CRP, ferritin, and LDH (only if LDH is elevated at baseline) levels may assist with the diagnosis and define the clinical course in regards to CRS/neurotoxicity. It is, therefore, recommended that CRP, ferritin, and LDH (if elevated at baseline) be monitored daily starting at Day 0 and continuing through hospitalization. In addition, lactate should be monitored as clinically indicated.

7.13.6 Post Treatment Assessment Period

After completing KTE-C19 infusion and discharged from the hospital all subjects will be followed in the post treatment assessment period. Counting from Day 0 (KTE-C19 infusion), subjects will return to the clinic at the following intervals.

- Week 2 (±2 days)
- Week 4 (± 3 days)
- Month 2 (± 1 week)
- Month 3 (± 1 week)

Subject will allow key sponsor contacts to continue to access medical records so that information related to subjects health condition and initial treatment response may be obtained. The following procedure will be completed for subjects as outlined in the SOA:

- **For subjects assigned to cohort 3, EQ-5D questionnaire (prior to any other assessments/procedures being performed)**
- **Neurological assessment including** MMSE
- PET-CT for disease assessment: If the PET-CT is not of high enough resolution, the scan must be repeated. Refer to the imaging charter for detailed instructions.
- **As applicable, bone marrow aspirate/biopsy to confirm response (i.e., for subjects presenting with bone marrow involvement prior to therapy or if new abnormalities in the peripheral blood counts or blood smear cause clinical suspicion of bone marrow involvement with lymphoma after treatment)**
- Physical exam
- Vital signs, including blood pressure, heart rate, oxygen saturation, and temperature
- Labs
    - Chemistry Panel
    - CBC with differential
    - β-HCG pregnancy test (serum or urine) on all women of child-bearing potential
    - Anti-KTE-C19 antibodies
    - Cytokine levels
    - Lymphocyte subsets
    - Anti-CD19 CAR+ T cells
    - RCR analysis
- **For subjects assigned to cohort 3, taper or discontinue levetiracetam as clinically indicated. See Section 6.3.4 and Section 6.4.3 for further details.**
- **For subjects assigned to cohort 3, lumbar puncture for collection of CSF samples at Week 4 (+/- 3 days)**
- Adverse/Serious Adverse Event reporting (refer to Section 9 for safety reporting guidelines)
- Concomitant medications documentation

If a subject is **discharged from the hospital and is** subsequently re-admitted to the hospital with any KTE-C19 related adverse event(s), the following **labs** will be **collected** as outlined in the SOA:

- Anti-CD19 CAR+ T cells on day of admission, then weekly, and on day of discharge
- Cytokine levels on day of admission, then weekly, and on day of discharge

At any time during the post treatment assessment period, if a subject did not respond to treatment (i.e., did not achieve a CR or PR) or progresses following a response **and is either not eligible for re-treatment or chooses not to pursue re-treatment**, the subject will proceed directly to the Month 3 visit and be followed for survival, **subsequent therapy** and disease outcomes in the long term follow-up period. **A PMBC sample (for anti-CD19 CAR+ T cells, etc) should be collected at the time of progression, prior to starting any subsequent anticancer therapy.**

7.13.7 Long Term Follow-up Period

All enrolled subjects will be followed in the long term follow-up period for survival and disease status, if applicable. Subjects will begin the long term follow-up period after they have completed the Month 3 visit of the post treatment assessment period (whether they have responded to treatment or went straight to the Month 3 visit due to disease progression)

- Every 3 months (± 2 weeks) through Month 18
- Every 6 months (± 1 month) between Month 24 - Month 60
- Beginning with year 6, Month 72 (± 3 months), subjects will return to the clinic 1 time annually up to 15 years.

The following procedures will be completed for subjects who are enrolled and receive KTE-C19, at the time points outlined in the SOA:

- **For subjects assigned to cohort 3, EQ-5D questionnaire (prior to any other assessments/procedures being performed)**
- Physical exam
- PET-CT/ Disease assessment through 24 months or until disease progression, whichever occurs first. **If subject's disease has not progressed by Month 24, disease assessments will continue to be performed per institutional standard of care.**
- Survival status
- Labs
  - CBC with differential
  - Anti-KTE-C19 antibodies (refer to Section 7.11)
  - Lymphocyte subsets
  - Anti-CD19 CAR+T cells
  - Replication-competent retrovirus (RCR) analysis
- Subsequent therapy for the treatment of NHL
- Targeted Adverse/Serious Adverse Event reporting (for 24 months or until disease progression whichever occurs first)
  - Including neurological, hematological, infections, autoimmune disorders, and secondary malignancies
- Targeted concomitant medication documentation (for **24 months or until** disease progression, **whichever occurs first**)
  - Including gammaglobulins, immunosuppressive drugs, anti-infectives, and vaccinations

Subjects may be contacted by telephone to confirm survival status and report targeted concomitant medication use.

If a subject progresses in the LTFU phase, the subject will continue to be followed for survival status and subsequent therapy for the treatment of NHL. A PMBC sample (for anti-CD19 CAR+ T cells, etc) should be collected at the time of progression, prior to starting any subsequent anticancer therapy.

The following procedures/assessments will be completed for subjects who are enrolled but do not receive KTE-C19, at the time points outlined in the SOA:

- Subsequent therapy for the treatment of NHL
- Survival status
- Disease assessment per standard of care
- Adverse/Serious Adverse Event reporting **and concomitant medication documentation** until 30 days after last procedure (e.g., leukapheresis, conditioning chemotherapy).

Should the subject fail to return to the clinic for a scheduled protocol specific visit, sites will need to make 2 attempts by a combination of telephone and mail to contact the subject. Sites must document both attempts to contact the subject. If a subject does not respond within 1 month after the second contact the subject will be considered lost to follow-up and no additional contact will be required.

7.13.8 Retreatment

Subjects who achieve a PR or CR will have an option to receive a second course of conditioning chemotherapy and KTE-C19 **under the following conditions:**

- **Subject had a PR or CR at the Month 3 disease assessment**
- **Subjects disease subsequently progressed greater than 3 months after KTE-C19 infusion**
- **CD19 tumor expression confirmed locally by biopsy after disease progression and prior to re-treatment**
- **Subject continues to meet the original study eligibility criteria with exception of prior KTE-C19 use in this study**
- **Subject has not received subsequent therapy for the treatment of lymphoma**
- **Subject did not experience a DLT in phase 1 or a comparable toxicity in phase 2**
- **Toxicities related to conditioning chemotherapy (fludarabine and cyclophosphamide), with the exception of alopecia, have resolved to ≤ grade 1 or returned to baseline prior to re-treatment**
- **Subject does not have known neutralizing antibodies (exception: if a non-neutralizing HAMA or HABA antibody develops subject may be retreated if they meet the original study eligibility criteria)**

The decision to administer re-treatment should be made in consultation with the Kite Medical Monitor. In addition, a discussion regarding benefits and risks of retreatment and including the potential need to undergo leukapheresis a second time for the manufacturing of KTE-C19 should occur with the subject prior to performing any study related procedures or treatment. This conversation should also be recorded in the subject's source document.

A maximum of 1 retreatment course may occur per subject. Subjects who are retreated will follow the same treatment schedule and procedural requirements per the initial treatment.

Subjects enrolled in phase 2 will receive the same KTE-C19 regimen at the original target dose. Subjects enrolled in phase 1 will receive the KTE-C19 regimen selected for phase 2 if they are retreated. If the phase 2 regimen has not yet been selected, subjects will receive the last KTE-C19 regimen that was determined safe by the SRT.

Allowance for retreatment is based on clinical experience reported in the 2 studies conducted at the pediatric (Lee 2015) and Surgery Branch (Kochenderfer 2015) of the NCI where 6 subjects in total have been re-treated upon progression. Three of the re-treated subjects (indolent lymphoma/leukemia) experienced durable responses to retreatment after an initial response and disease progression.

Schedule of Assessments

Procedures	**Screening**	**Enrollment/ Leukapheresis**	**Conditioning Chemotherapy Period**					**IP Administration Period**		**Post Treatment Follow-up (each visit calculated from Day 0)**			
Day	Within 28 days of enrollment	Within approx. 5 days of eligibility confirmation	-5	-4	-3	-2	-1	0	1 - 7	Week 2 (± 2 days)	Week 4 (± 3 days)	Month 2 (± 1 week)	Month 3 (± 1 week)
Medical history	X												
ECOG Performance Status	X												
EQ-5D Questionnaire (cohort 3 only)	**X**										**X**		**X**
Neurological assessment including Mini Mental Status Exam (MMSE)[5]	X							X	QOD [5]		X		X
ECG	X												
ECHO	X												
Archival/Fresh tumor [1]		X							between Day 7 & Day 14				
Brain MRI	X												
PET-CT/ disease assessment [2]	X										X		X
Physical exam	X									X	X	X	X
Vital signs (BP, HR, O_2 sat, temp)	X	X	X	X	X			X	X	X	X	X	X
Weight **(plus Height at screening)**	X	X											
Pregnancy test (serum or urine)	X												X
Lumbar Puncture[6]		X							X		**X**		
Blood draw for Chemistry panel	X	X	X	X	X			X	X	X	X	X	X
Blood draw for CBC w/differential	X	X	X	X	X			X	X	X	X	X	X
Blood draw for C-reactive protein (CRP)		X											
Blood draw for Anti-KTE-C19 antibody [3]		X									X		X
Blood draw for Lymphocyte subsets		X						X			X		X
Blood draw for Cytokines [5,7]		X						X	QOD [5]	X	X		
Blood draw for Anti-CD19 CAR+ T cells[7]		X						X	Day 7	X	X		X
Blood draw for RCR analysis [4]								X					X
Leukapheresis		X											
Fludarabine/Cyclophosphamide			X	X	X								
KTE-C19 infusion IV								X					
Tocilizumab[8]									**Day 2**				
Levetiracetam[9]								**Starting on Day 0**					
Adverse events/ Concomitant medication	X	→											

Schedule of Assessments (Footnotes)

[1] Archival/Fresh tumor sample: Either FFPE tumor block or up to 20 unstained slides. Fresh tumor sample for subjects who sign the optional portion of consent Archived and fresh tumor samples (if applicable) will be submitted to central laboratory after eligibility has been confirmed and prior to start of conditioning chemotherapy. Post treatment fresh tumor samples (if applicable) will be collected/submitted anytime between Day 7 and Day 14. **See Section 7.11 and 7.12 and central laboratory manual for details**

[2] PET-CT (Neck-Chest-Abdomen-Pelvis)**/disease assessment**: If PET-CT performed > 28 days prior to the initiation of conditioning chemotherapy or if subject receives any anti-cancer therapy between screening and conditioning chemotherapy, baseline scans must be repeated. Screening PET-CT should be completed as close to enrollment as possible. **As applicable, bone marrow aspirate/biopsy will be performed to confirm response (i.e., for subjects presenting with bone marrow involvement prior to therapy or if new abnormalities in the peripheral blood counts or blood smear cause clinical suspicion of bone marrow involvement with lymphoma after treatment). Bone marrow samples may also be collected and analyzed centrally for subjects who develop toxicities post KTE-C19. See Section 7.10 and Section 7.12**

[3] Blood draw for Anti-KTE-C19 antibody: Baseline antibody sample to be collected prior to start of leukapheresis. Post KTE-C19 antibody sample to be collected at Week 4 and Month 3 visits. See Section 7.11.for further details

[4] Blood draw for RCR: on Day 0 prior to administration of KTE-C19 and at Month 3, 6 and 12; then **collect** yearly for up to 15 years. Yearly **samples will only be analyzed** if positive at Month 3, 6, or 12.

[5] MMSE and Cytokines: prior to KTE-C19 infusion on Day 0, then on Day 1 and then every other day through hospitalization

[6] Lumbar Puncture: subjects with symptoms of CNS malignancy (e.g., new onset severe headaches, neck stiffness, or focal neurological findings) will have lumbar puncture performed at screening to assess cerebral spinal fluid for possible CNS involvement. Subjects with new onset grade ≥ 2 neurologic symptoms post KTE-C19 infusion will have lumber puncture performed to assess cerebral spinal fluid. In addition, subjects who sign the optional portion of the consent, will have lumbar puncture for the collection of CSF performed at baseline prior to KTE-C19 infusion and post KTE-C19 infusion (Day 5 ± 3 days). **For subjects assigned to cohort 3, lumbar punctures for collection of CSF samples will be performed at the following time points: after eligibility is confirmed and prior to start of conditioning chemotherapy, post KTE-C19 infusion on Day 5 (±3 days), and at the Week 4 visit (±3 days).**

[7] If a subject is discharged and then subsequently re-admitted to the hospital with any KTE-C19 related adverse events, blood samples for anti-CD19 CAR+ T cells and cytokines will be collected on day of admission, then weekly, and on day of discharge.

[8] **For cohort 3, administer tocilizumab at a dose of 8mg/kg IV over 1 hour (not to exceed 800mg) on Day 2. See Sections 6.3.4, 6.4.1, and 6.4.3 for further details.**

[9] **For cohort 3, administer levetiracetam at a dose of 750mg (PO or IV) BID starting on Day 0. See Sections 6.3.4 and 6.4.1 for further details.**

Schedule of Assessments (Long-Term Follow-up Period)

Procedure	**Long Term Follow-up Period (Each visit calculated from Day 0)**												
Visit Frequency	Month 6	Month 9	Month 12	Month 15	Month 18	Month 24	Month 30	Month 36	Month 42	Month 48	Month 54	Month 60	Month 72 and Annually Thereafter
EQ-5D Questionnaire	**X**												
Physical exam[1]	X	X	X	X	X	X							
PET-CT/**disease assessment**[2]	X	X	X	X	X	X	**X[2]**	**X[2]**	**X[2]**	**X[2]**	**X[2]**	**X[2]**	**X[2]**
Survival Status	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood draw for CBC w/differential [3]	X	X	X	X	X	X							
Blood draw for Anti-KTE-C19 antibody [4]													
Blood draw for Lymphocyte subsets [3]	X	X	X	X	X	X							
Blood draw for anti-CD19 CAR+ T cells[3]	X		X			X							
Blood draw for RCR analysis [5]	X		X			X		X		X		X	X
Targeted AE/SAEs [6]	X	X	X	X	X	X							
Targeted concomitant medication [7]	X	X	X	X	X	X							
Subsequent therapy for NHL[8]	X	X	X	X	X	X	X	X	X	X	X	X	X

[1] Physical exams will continue through Month 24

[2] PET-**CTs/disease assessments will** continue through Month 24 or until disease progression, whichever comes first**. If subject's disease has not progressed by Month 24, disease assessments will continue to be performed per standard of care.**

[3] Subjects will continue to provide samples for CBC w/diffs, lymphocyte subsets and anti-CD19 CAR+ T cells through Month 24

[4] Anti-KTE-C19 antibody samples: refer to Section 7.11

[5] RCR samples: collect and measured at Month 3, 6 and 12, **then collect yearly for up to 15 years. Yearly samples will only be analyzed if positive at Month 3, 6, or 12.**

[6] Targeted AEs/SAEs will be collected for 24 months or until disease progression (whichever occurs first)

[7] Targeted concomitant medications will be collected **for 24 months or until disease progression (whichever occurs first)**

[8] Subsequent therapy administered after KTE-C19 infusion for a subjects' disease such as non-study specified chemotherapy, immunotherapy, targeted agents, as well as stem cell transplant and radiation therapy must be collected until subject completes the long term follow up period, is considered lost to follow up, withdraws consent, or dies. **Subjects may be contacted by telephone to collect information about subsequent therapy for NHL and to assess survival status.**

8 Subject Withdraw

Subjects have the right to withdraw from the study at any time and for any reason without prejudice to their future medical care by the physician or at the institution.

Subjects can decline to continue to receive study required treatment and/or other protocol required procedures at any time during the study but continue to participate in the study. This is referred to as partial withdrawal of consent.

If partial withdrawal of consent occurs, the investigator must discuss with the subject the appropriate process for discontinuation from investigational product, study treatment or other protocol required therapies and must discuss options for continued participation, completion of procedures and the associated data collection as outlined in the SOA. The level of follow-up and method of communication should also be discussed between the research staff and the subject and documented in the source documents.

Withdrawal of full consent from a study means that the subject does not wish to receive further protocol required therapy or undergo procedures and the subject does not wish to continue further study follow-up. Subject data collected up to withdrawal of consent will be retained and included in the analysis of the study, and where permitted **by local regulations**, publically available data (death records) can be included after withdrawal of consent. The investigator is to discuss with the subject appropriate procedures for withdrawal from the study.

As part of the study sites may be asked to conduct searches of public records, such as those establishing survival status, if available, to obtain survival data for any subject for whom the survival status is not known. Sites may be also asked to also retrieve autopsy reports to confirm status of disease at the time of death.

The investigator and/or sponsor can also decide to withdraw a subject from the investigational product and/or other protocol-required therapies, protocol procedures, or the study as a whole or at any time prior to study completion.

8.1 Reasons for Removal from Treatment

Reasons for removal from protocol required investigational products or procedures include any of the following:

- Adverse Event
- Subject request
- Product not available
- Lost to Follow-up
- Death
- Decision by sponsor

8.2 Reasons for Removal from Study

Reasons for removal of a subject from the study are as follows:

- Subject withdrawal of consent from further follow-up
- Investigator decision
- Lost to follow-up
- Death

9 Safety Reporting

9.1 Adverse Events

An adverse event is defined as any untoward medical occurrence in a clinical trial subject. The event does not necessarily have a relationship with study treatment. The investigator is responsible for ensuring that any adverse events observed by the investigator or reported by the subject are recorded in the subject's medical record.

The definition of adverse events includes worsening of a pre-existing medical condition. Worsening indicates that the pre-existing medical condition has increased in severity, frequency, and/or duration or has an association with a worse outcome. A pre-existing condition that has not worsened during the study or involves an intervention such as elective cosmetic surgery or a medical procedure while on study, is not considered an adverse event.

Interventions for pretreatment conditions (such as elective cosmetic surgery) or medical procedures that were planned before study participation are not considered adverse events. Hospitalization for study treatment infusions or precautionary measures per institutional policy are not considered adverse events.

The term "disease progression" as assessed by measurement of malignant lesions on radiographs or other methods should not be reported as adverse events. Death due to disease progression in the absence of signs and symptoms should be reported as the primary tumor type (**e.g., B-Cell Lymphoma**).

For situations when an adverse event or serious adverse event is due to the disease under investigation report the signs and symptoms. Worsening of signs and symptoms of the malignancy under study should also be reported as adverse events in the appropriate section of the CRF.

The investigators clinical judgment is used to determine whether a subject is to be removed from treatment due to an adverse event. In the event a subject requests to withdraw from protocol required therapies or the study due to an adverse event, the subject should undergo the procedures outlined in the Month 3 visit of the SOA.

9.2 Reporting of Adverse Events

The investigator is responsible for ensuring that all adverse events observed by the investigator or reported by the subject that occur from enrollment (i.e., commencement of leukapheresis) through 3 months after treatment with KTE-C19 infusion are monitored and reported. After 3 months, targeted adverse events including (e.g., neurological, hematological, infections, autoimmune disorders, and secondary malignancies) **will be monitored and reported** for 24 months **after treatment with KTE-C19** or until disease progression, whichever occurs first.

For subjects who are enrolled but do not receive KTE-C19, the **adverse event** reporting period ends 30 days after the last **study specific** procedure (e.g., leukapheresis, conditioning chemotherapy).

The investigator must address the below for adverse events:

- Adverse event diagnosis or syndrome (if not known, signs or symptoms)
- Dates of onset and resolution
- Severity
- Assessment of relatedness to investigational product, conditioning chemotherapy or study procedures
- Action taken

Adverse event grading scale used will be the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. A copy of the grading scale can be downloaded from the CTEP home page (http://ctep.cancer.gov). Cytokine Release Syndrome events will also be reported using the grading scale outlined in Table 17 of Section 6.4.1.

In reviewing adverse events, investigators must assess whether the adverse event is possibly related to 1) the investigational product (KTE-C19), 2) conditioning chemotherapy or 3) any protocol required study procedure. The relationship is indicated by a yes or no response and entered into the CRF. A yes response should indicate that there is evidence to suggest a causal relationship between the study treatment or procedure and the adverse event. Additional relevant data with respect to describing the adverse event will be collected in the CRFs.

The investigator is responsible for reviewing laboratory test results and determining whether an abnormal value in an individual study subject represents a clinically significant change from the subject's baseline values. **In general, abnormal laboratory findings without clinical significance (based on the Investigator's judgment) are not to be recorded as adverse events. However, abnormal laboratory findings that result in new or worsening clinical sequelae, require therapy or adjustment in current therapy are considered adverse events. Where applicable, clinical sequelae (not the laboratory abnormality) are to be recorded as the adverse event.**

The investigator is expected to follow reported adverse events until stabilization or resolution**. If a subject begins a new anticancer therapy, the adverse event reporting period for non-serious adverse events ends at the time the new treatment is started.**

9.3 Definition of Serious Adverse Events

A serious adverse event is defined as an adverse event that meets at least 1 of the following serious criteria:

- Fatal
- Life threatening (places the subject at immediate risk of death)
- Requires in patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Congenital anomaly/birth defect
- Other medically important serious event

An adverse event would meet the criterion of "requires hospitalization" if the event necessitated an admission to a health care facility (e.g., overnight stay).

Events that require an escalation of care when the subject is already hospitalized should be recorded as a serious adverse event. Examples of such events include movement from routine care in the hospital to the ICU or if that event resulted in a prolongation of the existing planned hospitalization.

If an investigator considers an event to be clinically important, but it does not meet any of the serious criteria, the event could be classified as a serious adverse event with the criterion of "other medically important serious event."

9.4 Reporting of Serious Adverse Events and Non-Serious CRS events grade ≥ 3

The investigator is responsible for reporting all serious adverse events observed by the investigator or reported by the subject that occur after signing of the consent through 3 months after the KTE-C19 infusion. After 3 months, only serious targeted adverse events **(e.g., neurological, hematological,**

infections, autoimmune disorders, and secondary malignancies) observed by the investigator or reported by the subject will be reported for 24 months **after KTE-C19 infusion** or until disease progression, whichever occurs first. For subjects who screen fail or are enrolled but do not receive KTE-C19, the reporting period **for serious adverse events** ends 30 days after the last procedure (e.g., screen procedure, leukapheresis, conditioning chemotherapy).

All serious adverse events and non-serious CRS events ≥ grade 3 (Lee 2014; Table 17) must be submitted to Global Safety Advantage within 24 hours following the investigators knowledge of the event. All serious adverse events will be submitted by fax (Fax: 866-869-1551) or email globalsafetyadvantage@chiltern.com.

Serious adverse events and non-serious CRS events ≥ grade 3 may be reported by phoning GSA at 877-324-8200, however a phone call alone is insufficient; all events must be reported using a Serious Adverse Event Report Form submitted by fax or email within the time frames described in the protocol. Subsequently, all serious adverse events will be reported to the **health authorities per local reporting guidelines.**

Progression of the malignancy during the study should not be reported as a serious adverse event. Adverse events associated with disease progression may be reported as serious adverse event. If the malignancy has a fatal outcome within 3 months of the last day of the conditioning therapy or KTE-C19 then the event leading to death must be recorded as a serious adverse event with CTC grade 5.

Death must be reported if it occurs during the serious adverse event reporting period, irrespective of any intervening treatment.

Any death occurring after the first dose of chemotherapy, for the purpose of pre-conditioning, and within 3 months of the KTE-C19 infusion, regardless of attribution to treatment, requires expedited reporting within 24 hours. Any death occurring greater than 3 months after the KTE-C19 infusion requires expedited reporting within 24 hours only if it is considered related to treatment.

9.5 Pregnancy and Lactation

There is no relevant clinical experience with KTE-C19 in pregnant or lactating women, and animal reproductive studies have not been performed. Women of child bearing potential must have a negative pregnancy test prior to enrollment because of the potentially dangerous effects of the preparative chemotherapy on the fetus. This experimental therapy should not be administered to pregnant women or women who are breastfeeding.

If a pregnancy occurs in a female subject enrolled into the study, or a female partner of a male subject within 6 months of completing the KTE-C19 infusion, the pregnancy must be reported to the key sponsor contact. Information regarding the pregnancy and/or the outcome may be requested by the key sponsor.

In addition to reporting any pregnancies occurring during the study, investigators should monitor for pregnancies that occur after the last dose of KTE-C19 through 6 months for female subjects and for 6 months for the female partner of the male subjects.

The pregnancy should be reported to the key sponsor contact within 24 hours of the investigators knowledge of the pregnancy event.

If a lactation case occurs while the female subject is taking protocol required therapies report the lactation case to the key sponsor contact.

In addition to reporting a lactation case during the study, investigators should monitor for lactation cases that occur after the last dose of protocol required therapies through 6 months.

Any lactation case should be reported to the key sponsor contact within 24 hours of the investigator's knowledge of the event.

9.6 Safety Review Team and Dose-Limiting Toxicity

The SRT will be specifically chartered to review safety data during phase 1 of the study and make recommendations on further study conduct in phase 1 and progression to phase 2 based on the incidence of KTE-C19 DLT and review of serious adverse events.

Dose-limiting toxicity is defined as the following KTE-C19-related events with onset within the first 30 days following KTE-C19 infusion:

- Grade 4 neutropenia lasting longer than 21 days from the day of cell transfer
- Grade 4 thrombocytopenia lasting longer than 35 days from the day of cell transfer
- Any KTE-C19-related adverse event requiring intubation, including grade 4 confusion requiring intubation for airway protection is considered to be a DLT.
- All other grade 3 toxicities lasting more than 3 days and all grade 4 toxicities, with the exception of the following conditions which are not considered DLT's:
    - Aphasia/dysphasia or confusion/cognitive disturbance which resolves to grade 1 or less within 2 weeks and to baseline within 4 weeks
    - Fever grade 3
    - Myelosuppression (includes bleeding in the setting of platelet count less than 50 $x10^9$/L and documented bacterial infections in the setting of neutropenia), defined as lymphopenia, decreased hemoglobin, neutropenia and thrombocytopenia unless neutropenia and thrombocytopenia meet the DLT definition described above
    - Immediate hypersensitivity reactions occurring within 2 hours of cell infusion (related to cell infusion) that are reversible to a grade 2 or less within 24 hours of cell administration with standard therapy
    - Hypogammaglobulinemia grade 3 or 4

As noted in Section 6.4.1 CRS will be graded according to a revised grading system (Lee 2014). Adverse events attributed to CRS will be mapped to the overall CRS grading assessment for the determination of DLT.

During phase 1, approximately 6-24 subjects with DLBCL, PMBCL or TFL will be enrolled to evaluate the safety of KTE-C19 regimens.

Subjects in each cohort will be evaluated for DLTs within the first 30 days following the completion of their respective KTE-C19 infusion. The analysis of DLTs will be based on the DLT evaluable set as defined in Section 10.5. The SRT will make recommendations based on the incidence of DLT and overall safety profile of the KTE-C19 regimen. If the subject incidence of DLT is ≤ 1 of 6 subjects, cohort B1 may be explored or the study may proceed to phase 2 of the trial. This decision will be based on overall benefit/risk and available biomarker data.

However, if 2 of the 6 enrolled subjects present with a protocol defined DLT during phase 1, the SRT may recommend enrolling 2 additional sets of 3 subjects (up to 12 subjects in total) at the same dose that was administered in the first 6 subjects. In this scenario, progression to an additional cohort or to phase 2 of the study will proceed if ≤ 2 of the first 9 or if ≤ 3 of the 12 subjects present with a DLT.

If the subject incidence of DLT is > 2/6, >3/9, or >4/12 subjects, other KTE-C19 regimens may be explored in an additional 6-12 subjects (Figure 3). The same DLT rules apply as above.

9.7 Data Safety Monitoring Board

An independent DSMB will meet during the phase 2 portion of the study when 20 and 50 subjects **in the mITT set of** cohort 1 have had the opportunity to complete the 3-month disease assessment. The DSMB will review safety and efficacy data and be chartered to make trial conduct recommendations based on an analysis of risk vs. benefit.

The DSMB will also meet to review cohort 3 safety data when 20 subjects have been treated with KTE-C19 and have had the opportunity to be followed for 30 days. The DSMB may meet more often as needed. In addition, Kite Pharma or delegate will submit SAEs or suspected unexpected serious adverse reactions (SUSARs) to the DSMB chair for risk benefit analysis. The DSMB Chair will review reported SAEs at least monthly and SUSARs as soon as received.

9.8 Criteria to Pause Enrollment

As part of its oversight of the study, the DSMB also will assess criteria to pause enrollment after 10, 20, 30, and 50 subjects have been treated with KTE-C19 and have had the opportunity to be followed for 30 days. Enrollment will be paused if any of the following criteria is met:

1) Subject incidence of grade 5 KTE-C19 related adverse events within 30 days is >10%.

   OR

2) Subject incidence of the following grade 4 KTE-C19-related adverse events lasting more than 7 days is >33%:

   - Neurotoxicity
   - CRS (per Lee 2014 criteria)
   - Other non-hematological serious adverse event
   - Infection (treatment-related)

10 Statistical Considerations

Inferential testing will be performed for efficacy for phase 2 cohorts 1 and 2. For cohort 3, the primary efficacy objective will be to estimate the response rate with KTE-C19 treatment in subjects with refractory or relapsed DLBCL, PBMCL, or TFL.

10.1 Hypothesis

Cohort 1 and Cohort 2: This study is designed to differentiate between a treatment that has a true response rate of 20% or less and a treatment with a true response rate of 40% or more. The hypothesis is that the objective response rate to KTE-C19 in cohorts **1** and **2** is significantly greater than 20%.

Cohort 3: No hypothesis will be tested in cohort 3. Cohort 3 is designed to estimate the response rate in refractory or relapsed DLBCL, PMBCL, and TFL.

10.2 Study Endpoints

10.2.1 Primary

Phase 1: Incidence of adverse events defined as dose-limiting toxicities (DLT)

Phase 2: Objective Response Rate: ORR is defined as the incidence of either a complete response or a partial response by the revised IWG Response Criteria for Malignant Lymphoma (Cheson 2007) as determined by the study investigators. All subjects that do not meet the criteria for an objective response by the analysis cutoff date will be considered non-responders.

10.2.2 Secondary

Duration of Response: DOR for subjects who experience an objective response is defined as the date of their first objective response (which is subsequently confirmed) to disease progression per the revised IWG Response Criteria for Malignant Lymphoma (Cheson 2007) or death regardless of cause. Subjects not meeting the criteria for progression or death by the analysis data cutoff date will be censored at their last evaluable disease assessment date and their response will be noted as ongoing.

Objective response rate among subjects in phase 1 will be summarized.

Objective response rate per IRRC (phase 2): objective response rate per IRRC is defined as the incidence of either a complete response or a partial response by the revised IWG Response Criteria for Malignant Lymphoma (Cheson, 2007) as determined by the IRRC. All subjects that do not meet the criteria for an objective response by the analysis data cutoff date will be considered non-responders.

Progression Free Survival: PFS is defined as the time from the KTE-C19 infusion date to the date of disease progression per the revised IWG Response Criteria for Malignant Lymphoma (Cheson 2007) or death from any cause. Subjects not meeting the criteria for progression by the analysis data cutoff date will be censored at their last evaluable disease assessment date.

Overall Survival: OS is defined as the time from KTE-C19 infusion to the date of death. Subjects who have not died by the analysis data cutoff date will be censored at their last contact date.

Incidence of adverse events and clinical significant changes in safety lab values, **including subgroup analyses of subjects in cohort 3 treated prophylactically for safety management.**

Changes over time in the EQ-5D scale score and EQ-5D VAS score for subjects assigned to cohort 3.

Incidence of anti-KTE-C19 antibodies, levels of anti-CD19 CAR+ T cells in blood and levels of cytokines in serum will be summarized.

10.2.3 Exploratory Endpoints

Objective Response Rate and duration of second response among subjects retreated with KTE-C19 (Section 7.13.8)

Objective Response Rate and duration of response as determined by IWG Response Criteria for Malignant Lymphoma (Cheson 2014)

Investigation of potential biomarker development based on assessment of blood cells, tumor cells and the proposed actions of the investigational product.

10.3 Sample Size Considerations

The anticipated enrollment in this study is approximately **148** to **166** subjects.

Six to 12 subjects will be enrolled into each cohort in phase 1 of this study.

If the study proceeds to phase 2, **approximately** 72 subjects will be enrolled into cohort 1 and **approximately 20** subjects will be enrolled into cohort 2. **Up to 50 subjects will be enrolled into cohort 3.**

The primary efficacy endpoint and all analyses based on the objective response (objective response, duration of response, progression-free survival) in the phase 1 and phase 2 portions of the study will be based on a mITT population consisting of all subjects who receive the target dose of KTE-C19.

Inferential testing will be performed for efficacy for phase 2 cohorts 1 and 2. For cohort 3, the primary efficacy objective will be to estimate the response rate with KTE-C19 treatment in subjects with refractory or relapsed DLBCL, PBMCL, or TFL.

10.3.1 Phase 2, Cohorts 1 and 2

This study uses a single arm design to test for an improvement in response rate in the DLBCL cohort (approximately n=72) and in cohorts 1 and 2 combined (n=92). For the test of efficacy this study has ≥ 90% power to distinguish between an active therapy with a 40% true response rate from a therapy with a response rate of 20% or less with a 1-sided alpha level of 0.025.

The overall 1-sided alpha level of 0.025 will be divided between the inference on cohort 1 and the inference in **cohorts 1 and 2 combined** using the methodology described in Song 2007 and Wang 2007. The objective response for cohort 1 will be tested at a 1-sided alpha level of 0.0220 and the objective response in **cohort 1 and 2 combined** will be tested at a 1-sided alpha level of 0.0075.

Within cohort 1, 2 interim and 1 primary analyses will be performed.

- Interim analysis 1 will be conducted after 20 subjects in the mITT set have had the opportunity to be evaluated for response 3 months after the KTE-C19 infusion. This interim analysis will be for futility only. **This futility analysis is based on a rho (parameter 0.35) beta spending function, with a nominal alpha level for the assessment of futility of 0.393. If the criteria for futility are not met,** accrual to phase 2 will continue. Under the null hypothesis, the likelihood of stopping for futility at this analysis is 63%.

- Interim analysis 2 will be conducted after 50 subjects **in the mITT set** have had the opportunity to be evaluated for response 3 months after the KTE-C19 infusion. This interim analysis will assess early demonstration of efficacy. **This interim analysis is based on a Pocock boundary of the Lan-DeMets family of alpha spending functions. The nominal alpha level for the assessment of efficacy for this analysis is 0.017.** Under the alternative hypothesis, the likelihood of achieving the criteria for early efficacy is 84%. **If the criteria for early efficacy are not met at this analysis, the planned primary analysis of cohort 1 will occur when 72 subjects in the mITT set of cohort 1 have had the opportunity to be followed for 6 months after the KTE-C19 infusion.**

- The primary analysis of cohort 1 will occur after **72** subjects in **the mITT set** have had the opportunity to be assessed for response 6 months after the KTE-C19 infusion. **The nominal alpha level for the assessment of efficacy at the primary analysis is 0.011.**

Accrual to the study will continue during interim analysis 1 and interim analysis 2 of cohort 1.

For cohorts 1 and 2 combined, 1 primary analysis will be performed when **72 subjects in the mITT set in** cohort 1 and **20 subjects in the mITT set in cohort 2** have had the opportunity to be assessed for

response 6 months after the KTE-C19 infusion. This testing will be performed at a 1-sided alpha level of 0.0075. Descriptive confidence intervals about the objective response rates within cohorts 1 and 2 will be presented with the inferential analysis of **cohorts 1 and 2 combined.**

As indicated above, inferential testing of cohort 1 will occur when 72 subjects in the mITT set in cohort 1 have had the opportunity to be followed for 6 months after the KTE-C19 infusion. The efficacy data from any additional subjects (beyond 72) enrolled into cohort 1 will be analyzed descriptively. Similarly, inferential testing of cohorts 1 and 2 will occur when 72 subjects in the mITT set of cohort 1 and 20 subjects in the mITT set of cohort 2 have had the opportunity to be followed for 6 months following the KTE-C19 infusion. The efficacy data from any additional subjects (beyond 92) enrolled into cohorts 1 and 2 will be analyzed descriptively.

The derivation of the alpha levels for the test of cohort 1 and the overall study population **were originally obtained under the assumption of 40 subjects enrolled into cohort 2. These original derivations are retained in this protocol amendment as they result in a more conservative alpha level for the test of cohort 1**. .

This procedure preserves the designated alpha level (1-sided) of 0.025 and has ≥ 90% power. Simulation (10000 replicates) via R version 3.1.0 and EAST version 6.3 were used to evaluate the operating characteristics of this design.

10.3.2 Phase 2, Cohort 3

Phase 2 cohort 3 uses a single arm design to estimate the response rate in subjects with refractory or relapsed DLBCL, PMBCL, or TFL treated with KTE-C19. The two-sided 95% confidence intervals at a range of target response rates are provided in Table 21. There are no criteria on the proportion of refractory versus relapsed subjects who will be enrolled into cohort 3 and hence a range of potential observed response rates are presented in Table 21. As indicated, with a sample size of 50 subjects the maximum width of the 95% confidence interval about response rate will be no greater than 29.

Table 21. 95% Confidence Intervals Corresponding to the Observed Objective Response Rate in Cohort 3

Observed Response Rate	95% Confidence Interval
40%	(27%, 55%)
50%	(36%, 65%)
60%	(45%, 73%)
70%	(56%, 82%)
80%	(67%, 90%)

10.4 Statistical Assumptions

Phase 1 and cohorts 1 and 2 of this trial will enroll subjects with chemo-refractory lymphoma, as evidenced by failure to achieve even a transient or partial response to prior biologic and combination chemotherapy or by early recurrence after ASCT.

Treatment outcomes for subjects refractory to primary therapy or non-responsive to second line therapy are provided in Section 2.1, Table 1. As indicated, the response to salvage therapy for these subjects ranged from 0% to 26%. **Additionally, a retrospective review of data in refractory DLBCL from 4 institutions (Crump, 2016) indicate a response rate of 26% among 597 refractory subjects.** Based on these data, it is anticipated that the historical control for the objective response rate in the chemo-refractory population targeted in this study will be approximately 20%.

10.5 Analysis Subsets

Phase 1:

Depending on the dosing cohort and results of the phase 1 portion of the study, KTE-C19 may be:

- administered as a single infusion at a target dose of 2 x 10^6 anti-CD19 CAR+ T cells/kg (±20%). For subjects weighing greater than 100 kg, a maximum flat dose of 2 x 10^8 anti-CD19 CAR+ T cells will be administered. A minimum dose of 1 x 10^6 anti-CD19 CAR+ T cells/kg may be administered; or
- administered as a single infusion at a target dose of 1 x 10^6 anti-CD19 CAR+ T cells/kg (± 20%) in the phase 2 portion of the study. In this case, for subjects weighing greater than 100 kg, a maximum flat dose of 1 x 10^8 anti-CD19 CAR+ T cells will be administered. A minimum dose of 0.5 x 10^6 anti-CD19 CAR+ T cells/kg may be administered.

The DLT evaluable set (phase 1 only), defined for each dosing cohort in phase 1, will include subjects treated in the phase 1 dosing cohort who:

- received the target and were followed for at least 30 days after the anti-CD19 CAR+ T cell infusion; or
- received a dose of anti-CD19 CAR+ T cells lower than the target for that cohort and experienced a DLT during the 30 day post-infusion period.

If needed, more subjects will be enrolled to achieve 6 DLT evaluable subjects at the target dose for each cohort.

Safety set: the safety set is defined as all subjects treated with any dose of KTE-C19.

Phase 2:

In the phase 2 portion of the study, subjects are to be dosed at a target of 2 x 10^6 anti-CD19 CAR+ T cells/kg. A minimum dose of 1 x 10^6 anti-CD19 CAR+ T cells/kg may be administered. For subjects weighing greater than 100 kg, a maximum flat dose of 2 x 10^8 anti-CD19 CAR+ T cells will be administered. Subjects are considered to have received the target dose if they receive 1 x 10^6 anti-CD19 CAR+ T cells/kg up to 2 x 10^6 anti-CD19 CAR+ T cells/kg or, if the subject weighs more than 100 kg, the subject receives 2 x 10^8 anti-CD19 CAR+ T cells.

Modified Intent to Treat Set (mITT): the modified intent to treat set will consist of all subjects enrolled and treated with KTE-C19 **at a dose of at least 1 x 10^6 anti-CD19 CAR+ T cells/kg.**

This analysis set will be used for all analyses of objective response and endpoints based on objective response (objective response, duration of response, progression-free survival) for both the phase 1 and phase 2 portions of the study).

Safety set: the safety set is defined as all subjects treated with any dose of KTE-C19.

Full Analysis set (FAS): the full analysis set will consist of all enrolled subjects and will be used for the summary of subject disposition, sensitivity analyses of objective response rate and duration of response, and subject listings of deaths.

10.6 Access to Individual Subject Treatment Assignments

This is a single arm, open-label study and subjects and investigators will be aware of treatment received. Data handling procedures for the phase 2 portion of the study will be devised to reduce potential sources of bias and maintain the validity and credibility of the study. These procedures will be outlined in the study statistical analysis plan, DSMB charter, and Trial Integrity Document.

10.7 Interim Analysis

10.7.1 Interim Analysis and Early Stopping Rules

The SRT will be chartered to review safety during phase 1 of the study only and make recommendations on further study conduct in phase 1 and progression to phase 2.

An independent DSMB will be formed to review accumulating safety and efficacy data 2 times during the phase 2 portion of the study, when 20 and 50 subjects **in the mITT set** in cohort 1 have had the opportunity to complete the 3 month disease assessment. **Additionally, the DSMB will review safety data when 20 subjects treated in cohort 3 have had the opportunity to be followed for 30 days.**

The DSMB will also monitor criteria to pause enrollment (see Section 9.8).

10.7.2 Safety Interim Analysis

The DSMB will review AE and SAE information on a regular basis throughout subject treatment in phase 2 of the study. The DSMB may request additional safety data or modifying the study conduct. The sponsor may request additional reviews by the DSMB if safety concerns are identified. Data submitted to the DSMB may be monitored or unmonitored to facilitate timely DSMB review.

10.7.3 Efficacy Interim Analysis

Within cohort 1, 2 interim analyses will be performed.

- Interim analysis 1 will be conducted after 20 subjects in the mITT set have had the opportunity to be evaluated for response 3 months after the KTE-C19 infusion. This interim analysis will be for futility only. **This futility analysis is based on a rho (parameter 0.35) beta spending function, with a nominal alpha level for the assessment of futility of 0.393. If the criteria for futility are not met, accrual to phase 2 will continue.** Under the null hypothesis, the likelihood of stopping for futility at this analysis is 63%.

- Interim analysis 2 will be conducted after 50 subjects in the mITT set have had the opportunity to be evaluated for response 3 months after the KTE-C19 infusion. This interim analysis will assess early stopping for efficacy. **This interim analysis is based on a Pocock boundary of the of the Lan-DeMets family of alpha spending functions. The nominal alpha level for the assessment of efficacy for this analysis is 0.017. Under the alternative hypothesis, the**

likelihood of achieving the criteria for early efficacy is 84%. If the criteria for early efficacy are not met at this analysis, the planned primary analysis of cohort 1 will occur when 72 subjects in the mITT set of cohort 1 have had the opportunity to be followed for 6 months after the KTE-C19 infusion.

10.8 Planned Method of Analysis

The primary efficacy analyses of cohort 1 will be performed when **72 subjects in the mITT set of cohort 1 have** had the opportunity to be evaluated for response 6 months after the KTE-C19 infusion. The primary analysis of **cohorts 1 and 2 combined** will be performed when 72 subjects **in the mITT set of cohort 1 and 20 subjects in the mITT set of cohort 2 have** had the opportunity to be evaluated for response at 6 months after the target KTE-C19 infusion. **The primary analysis of cohort 3 will occur after all treated subjects have had the opportunity to be followed for 6 months**. Additional analyses may occur after the primary analysis. These additional analyses will be descriptive and will occur after inferential testing has been performed. The final analysis will occur when all subjects have completed the study.

Descriptive analyses of the phase 1 portion of the study **and phase 2 cohort 3** may occur at any time.

The primary endpoint of objective response rate for all analyses (futility, interim, and primary) will be based on investigator review of disease assessments in the mITT set. **For cohorts 1 and 2**, sensitivity analyses of objective response rate based on central radiologic review of disease assessments will be performed.

Analyses of efficacy endpoints will be summarized by study phase, **for cohort 1 alone, for cohorts 1 and 2 combined, and for cohort 3 alone**. Analyses of safety endpoints will be evaluated by **study phase, cohort, cohort 1 and 2 combined.**

10.8.1 Objective Response Rate

The incidence of objective response and exact 2-sided 95% confidence intervals will be generated. **For cohorts 1 and 2,** an exact binomial test will be used to compare the observed response rate to a response rate of 20%.

10.8.2 Duration of Response

The competing-risk analysis method (**Pepe, 1991, Fine and Gray, 1999**) will be used to estimate the cumulative incidence of relapse. The cumulative incidence of relapse in the presence of non-disease related mortality (the competing risk) will be estimated along with 2-sided 95% confidence intervals at 3-month intervals.

10.8.3 Progression Free Survival

Kaplan-Meier estimates and 2-sided 95% confidence intervals will be generated for progression-free survival time. Estimates of the proportion of subjects alive and progression-free at 3-month intervals will be provided.

10.8.4 Overall Survival

Kaplan-Meier estimates and 2-sided 95% confidence intervals will be generated for OS. Estimates of the proportion of subjects alive at 3-month intervals will be provided.

10.8.5 Safety

Subject incidence rates of adverse events including all, serious, fatal, CTCAE version 4 grade 3 or higher and treatment related AEs reported throughout the conduct of the study will be tabulated by preferred term and system organ class. Changes in laboratory values and vital signs will be summarized with descriptive statistics. The incidence of concomitant medications will be summarized.

For cohort 3, the incidence and severity of CRS and neurotoxicity may be compared to the rates in cohorts 1 and 2 combined with a binomial test.

Tables and/or narratives of deaths though the long term follow-up and treatment related SAEs will be provided.

10.8.6 Long Term Data Analysis

All subjects will be followed for survival for up to approximately 15 years after the last subject receives KTE-C19. No formal hypothesis testing will be performed based on data obtained after the cutoff for the primary analysis. Descriptive estimates of key efficacy and safety analyses may be updated to assess the overall treatment profile.

11 Regulatory Obligations

11.1 Independent Review Board /Independent Ethics Committee

A copy of the protocol, ICF and any additional subject or trial information such as subject recruitment materials must be submitted to each sites respective IRB/IEC for approval. Once approval is obtained from the IRB/IEC, all documents must be provided to the key sponsor contact before subject recruitment can begin.

The investigator must also receive IRB/IEC approval for all protocol and ICF changes or amendments. Investigators must ensure that ongoing/continuous IRB/IEC approval (ie, annual approval) is provided throughout the conduct of the study. Copies of IRB/IEC approval are to be forwarded to the key sponsor contact for archiving.

During the course of the study, investigators are to submit site specific and study serious adverse events (provided to the site by the key sponsor contact) along with any protocol deviations to their IRB/IEC in accordance with their respective IRB/IEC policies.

11.2 Subject Confidentiality

Subject confidentiality must be contained at all material submitted to the key sponsor contact. The following rules are to be applied.

- Subjects will be identified by a unique identification number
- Date of birth **or year of birth/age at time of enrollment** will be reported according with local laws and regulations

For reporting of serious adverse events, subjects will be identified by their respective subject identification number, initials and data of birth **or year of birth** (as per their local reporting requirements for both initials and date of birth)

Per federal regulations and ICH/GCP guidelines, investigators and institutions are required to permit authorization to the sponsor, CRO, IRB/IEC and regulatory agencies to subject's original source

documents for verification of study data. The investigator is responsible for informing potential subjects that such individuals will have access to their medical records which includes personal information.

11.3 Investigator Signatory Obligations

Each clinical study report will be signed by the coordinating investigator. The coordinating investigator will be identified by Kite Pharma under the following criteria:

- A recognized expert in the disease setting
- Provided significant contributions to the design or analysis of study data
- Participate in the study and enrolled a high number of eligible subjects

12 Protocol Amendments and Termination

If the protocol is amended, the investigators agreement with the amendment and the IRB/IEC approval of the amendment must be obtained. Documentation acknowledging approval from both parties are to be submitted to the key sponsor contact.

Both Kite pharma and the investigator reserve the right to terminate the investigators participation in the study as per the terms of the agreement in the study contract. The investigator is to provide written communication to the IRB/IEC of the trial completion or early termination and provide the CRO with a copy of the correspondence.

Kite Pharma reserves the unilateral right, at is sole discretion, to determine whether to manufacture KTE-C19 T cells and provide them to sites and subjects after the completion of the study and before treatment becomes commercially available.

13 Study Documentation and Archive

The investigator will maintain a list of qualified staff to whom study responsibilities have been delegated. These individuals authorized to fulfil these responsibilities should **be** outlined and included in the Delegation of Authority Form.

Source documents are original documents, data and records for which the study data are collected and verified. Example of such source documents may include, but are not limited to, hospital records and patient charts, laboratory, pharmacy, radiology and records, subject diaries, microfiches, correspondence and death registries. Case report form entries may be considered as source data if the site of the original data collection is not available. However, use of the CRFs as source documentation as a routine practice is not recommended.

The investigator and study staff are responsible for maintaining a comprehensive and centralize filing system of all subject records that are readily retrieved to be monitored and or audited at any time by the key sponsor contact, regulatory authorities and IRB/IECs. The filing system will include at minimum:

- Subject content including ICFs and subject identification lists
- Protocols and protocol amendments, investigator brochure, copies of pre-study documentation, and all IRB/IEC and sponsor communication
- Proof of receipt, experimental treatment flow records and experimental product related correspondence.

Original source documents supporting entries into CRFs must be maintained at the site and readily available upon request. No study documents should be discarded without prior written agreement between Kite Pharma and the investigator. Should storage no longer be available to archive source

documents or must be moved to an alternative location, the research staff should notify the key sponsor contact prior to the shipping the documents.

14 Study Monitoring and Data Collection

The key sponsor contact, monitors, auditors or regulatory inspectors are responsible for contacting and visiting the investigator for the purpose of inspecting the facilities and verifying source documents and records assuring that subject confidentially is respected.

The monitor is responsible for source document verification of CRF data at regular intervals during the study. Protocol adherence, accuracy and consistency of study conduct and data collection with respect to local regulations will be confirmed. Monitors will have access to subject records as identified in Section 13.

By signing the investigator agreement, the investigator agrees to cooperate with the monitor to address and resolve issues identified during monitoring visits.

In accordance with ICH GCP and the audit plan, a site may be chosen for a site audit. A site audit would include, but is not limited to, an inspection of the facility (ies), review of subject and study related records, and compliance with protocol requirements as well as ICH GCP and applicable regulatory policies.

All data will be collected in an electronic CRF system. All entries must be completed in English and concomitant medications should be identified by tradenames. For further details surrounding the completion of CRFs, please refer to the CRF completion guidelines.

15 Publication

Authorship of publications from data generated in study KTE-C19-101 will be determined based on the uniform requirements for manuscripts submitted to biomedical journals (as outlined in the International Committee of Medical Journal Editors December 2013) which states:

- Authorship should be based on
  - Substantial contributions to the conception or design of the work, acquisition of data, analysis, or interpretation of data for the work; AND
  - Drafting the article or revising it critically for important intellectual content; AND
  - Final approval of the version to be published; AND
  - Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work re appropriately investigated or resolved

When a large, multicenter group has conducted the work, the group should identify the individuals who accept direct responsibility for the manuscript. This individual should fully meet the criteria for authorship defined above.

Funding, collection of data or general supervision of the research alone or in combination does not qualify an individual for authorship.

Any publication, in any form, that is derived from this study must be submitted to Kite Pharma for review and approval. The study contract between the institution, principal investigation and Kite Pharma or its delegate will outline the requirements for publication review.

16 Compensation

Kite Pharma will provide compensation for study related illness or injury pursuant to the information outlined in the injury section of the ICF.

References

Abe Y, Choi I, Hara K, et al. Case Report – Hemophagocytic syndrome: a rare complication of allogeneic nonmyeloablative hematopoietic stem cell transplantation. *Bone Marrow Transplantation* 2002 Aug;29:799-801.

Ardeshna K, Kakouros N, Qian W, et al. Conventional second-line salvage chemotherapy regimens are not warranted in patients with malignant lymphomas who have progressive disease after first-line salvage therapy regimens. *Br J Haematol* 2005 Aug;130(3):363-72.

Barrett D, Teachey D, Grupp S. Toxicity management for patients receiving novel T-cell engaging therapies. *Current Opinion in Pediatrics* 2014 Feb;(26)1:43-49.

Better M, Pugach O, et al. Rapid cell expansion (RACE) technology for production of engineered autologous T-cell therapy: Path toward manageable multicenter clinical trials in aggressive NHL with anti-CD19 CAR. ASCO 2014; Chicago, Illinios. Poster Presentation; #3079.

Blanc V, Bousseau A, Caron A, et al. SAR3419: an anti-CD19-maytansinoid immunoconjugate for the treatment of B-cell malignancies. *Clin Cancer Res* 2011;17:6448–6458.

Chen F, Teachey D, Pequignot E, et al. Measuring IL-6 and sIL-6R in serum form patients treated with tocilizumab and/or siltuximab following CAR T cell therapy. *J Immunol Methods* 2016 April;pii:S0022-1759(16)30054-0.

Cheson B, Pfistner B, Juweid M, et al. Revised response criteria for malignant lymphoma. *J Clin Oncol* 2007;25(5):579.

Cheson B, Fisher R, Barrington S, et al. Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification. *J Clin Oncol* 2014;32(27):3059-3067.

Davila M, Riviere I, Wang X, et al. Efficacy and Toxicity Management of 1928z CAR T Cell Therapy in B Cell Acute Lymphoblastic Leukemia. *Sci Transl Med* Feb 2014;6(224):224ra25.

Dunleavy K, Pittaluga S, Maeda L, et al. Dose-Adjusted-EPOCH-R Therapy in Primary Mediastinal B-cell Lymphoma. *N Eng J Med* 2013 April;368(15):1408-16.

Ferreria R, Vastert S, Abinun M, et al. Hemophagocytosis during fludarabine-based SCT for systemic juvenile idiopathic arthritis. *Bone Marrow Transplantation* 2006;38:249-251.

Fine J, Gray RA. Proportional hazards model for the subdistribution of a competing risk. *J American Statistical Assoc* 1999;94(446):496-509.

Flammiger A, Fiedler W, Bacher U, et al. Imbalance of TNF-a and soluble TNF receptor 1 in a patient with macrophage activation syndrome: potential implications for diagnostics and treatment. *Acta Haematol* 2012;128(2):69-72.

Flowers C, Sinha R, Vose J. Improving outcomes for patients with diffuse large B-cell lymphoma. *Cancer J Clin* 2010;60; 393-408.

Frey N, et al. Refractory Cytokine Release Syndrome in Recipients of Chimeric Antigen Receptor (CAR) T Cells. 2014 ASH Meeting and Exposition: Abstract 2296.

Gabay C, Lamacchia C, Palmer G. IL-1 pathways in inflammation and human diseases. *Nat Rev Rheumatol* 2010;6(4):232-241.

Gattinoni L, Finkelstein S, Klebanoff C, et al. Removal of homeostatic cytokine sinks by lymphodepletion enhances the efficacy of adoptively transferred tumor-specific $CD8^+$ T cells. *JEM* October 2005;202(7):907-912.

Hitz F, Connors J, Gascoyne R. Outcome of Patients with Chemotherapy Refractory and Early Progressive Diffuse Large B Cell Lymphoma After R-CHOP Treatment. *Blood* (ASH Annual Meeting Abstracts, Poster Session) 2010;116:Abstract 1751.

Jordan M, Allen C, Weitzman S, et al. How I treat hemophagocytic lymphohistiocytosis. *Blood* 2011 Oct;118(15):4041-4052.

Josting A, Rueffer U, Franklin J, et al. Prognostic factors and treatment outcome in primary progressive Hodgkins Lymphoma: a report from the German Hodgkin study group. *Blood* 2000 August;96(4):1280-1286.

Kershaw M, Westwood A, Darcy P. Gene-engineered T cells for cancer therapy. *Nature Reviews Cancer* 2013;13(8):525-541.

Khouri I, Keating M, Korbling M, et al. Transplant-Lite: Induction of Graft-Versus-Malignancy Using Fludarabine-Based Nonablative Chemotherapy and Allogeneic Blood Progenitor-Cell Transplantation as Treatment for Lymphoid Malignancies. *J Clin Oncol* 1998 August;16(8):2817-2824.

Klebanoff C, Knong H, et al. Sinks, supressors and antigen presenters: how lymphodepletion enhances T cell-mediated tumor immunotherapy. Trends Immunol 2005 Feb;26(2):111-117.

*Klein J, Moeschberger M. Survival Analysis: Techniques for Censored and Truncated Data. New York. Springer, 200*5.

Kochenderfer J, Feldman S, Zhao Y, et al. Construction and Pre-clinical Evaluation of an Anti-CD19 Chimeric Antigen Receptor. *J Immunother* 2009 September;32(7):689–702.

Kochenderfer J, Yu Z, Frasheri D, et al Adoptive transfer of syngeneic T cells transduced with a chimeric antigen receptor that recognizes murine CD19 can eradicate lymphoma and normal B cells. *Blood* 2010a Nov;116(19):3875–3886.

Kochenderfer J, Dudley M, Feldman S, et al. B-cell depletion and remissions of malignancy along with cytokine-associated toxicity in a clinical trial of anti-CD19 chimeric-antigen-receptor–transduced T cells. *Blood* 2012;119:2709-2720.

Kochenderfer J, et al. Effective Treatment of Chemotherapy-Refractory Diffuse Large B-Cell Lymphoma with Autologous T Cells Genetically-Engineered To Express an Anti-CD19 Chimeric Antigen Receptor. *Blood* 2013 November;122(21):168.

Kochenderfer J, Dudley M, Kassim S, et al. Chemotherapy-Refractory Large-cell and Indolent B-cell Malignancies Can Be Effectively Treated with Autologous T Cells Expressing Anti-CD19 Chimeric Antigen Receptor. *J Clin Oncol* 2015 Feb;33(6):540-9.

Kowolik C, Topp M, Gonzalez S, et al. CD28 costimulation provided through a CD19-specific chimeric antigen receptor enhances in vivo persistence and antitumor efficacy of adoptively transferred T cells. *Cancer Res* 2006;66(22):10995-11004.

Kuruvilla J, Pintilie M, Tsang R, et al. Salvage chemotherapy and autologous stem cell transplantation are inferior for relapsed or refractory primary mediastinal large B-cell lymphoma compared with diffuse large B-cell lymphoma. Leuk Lymphoma 2008 July;49(7):1329-1336.

Lackner H, Urban C, Sovinz P, et al. Hemophagocytic lymphohistiocytosis as severe adverse event of antineoplastic treatment in children. *Haematologica* 2008;93(2):291-294.

La Rosee P. Treatment of hemophagocytic lymphohistiocytosis in adults. *American Society of Hematology Educ Program* 2015;2015:190-196.

Lee D, Gardner R, Porter D, et al. How I treat: current concepts in the diagnosis and management of cytokine release syndrome. *Blood* 2014 July;124(2):188-95.

Lee D, Kochenderfer J, Stetler-Stevenson M, et al. T cells expressing CD19 chimeric antigen receptors for acute lymphoblastic leukaemia in children and young adults: a phase 1 dose-escalation trial. *Lancet* 2015;185(9967):517-28.

Lyman G, Bohlke K, Khorana A, et al. Venous Thromboemolism Prophylaxix and Treatment in Patients with Cancer: American Society of Clinical Oncology Clinical Practice Guideline Update 2014. *J Clin Oncol* 2015 Feb;33(6):654-6.

Matasar M, Czuczman M, Rodriguez M, et al. Ofatumumab in combination with ICE or DHAP chemotherapy in relapsed or refractory intermediate grade B-cell lymphoma. *Blood* 2013 July;122(4):499-506.

Maude S, Teachey D, Porter D, et al. CD19-targeted chimeric antigen receptor T-cell therapy for acute lymphoblastic leukemia. *Blood* 2015 June;125(26):4017-4023.

Maude S, Barrett D, Teachey D, et al. Managing cytokine release syndrome associated with novel T cell-engaging therapies. *The Cancer Journal* 2014 (March/April);20(2):119-122.

Moskowitz C, Bertino J, Glassman J, et al. Ifosfamide, carboplatin, and etoposide: a highly effective cytoreduction and peripheral-blood progenitor-cell mobilization regimen for transplant-eligible patients with non-Hodgkin's lymphoma. *J of Clinical Oncology* 1999;17(12):3776-85.

Moye L, Deswal A. Trials within trials: confirmatory subgroup analyses in controlled clinical experiments. *Controlled Clinical Trials* 2001;22:605-619.

Nagle S, Woo K, Schuster S, et al. Outcomes of patients with relapsed/refractory diffuse large B-cell lymphoma with progression of lymphoma after autologous stem cell transplantation in the rituximab era. *Am J Hematol* 2013 Oct;88(10):890-4.

National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology; Non-Hodkin's Lymphomas, Version 1.2014. (http://www.nccn.org/professionals/physician_gls/f_guidelines.asp#nhl) Accessed January 22, 2014.

Nicholson I, Lenton K, Little D, et al. Construction and characterisation of a functional CD19 specific single chain Fv fragment for immunotherapy of B lineage leukaemia and lymphoma. *Mol Immunol* 1997;34(16–17):1157-1165.

O'Brien S, Kantarjian H, et al. Results of the Fludarabine and Cyclophosphamide Combination Regimen in Chronic Lymphocytic Leukemia. *J Clin Oncol* March 2001;19(5):1414-1420.

Pepe, M. Inference for events with dependent risks in multiple endpoint studies. *J American Statistical Assoc* 1991;86:770-778.

Phillip T, Guglielmi C, Hagenbeek A, et al. Autologous bone marrow transplantation as compared with salvage chemotherapy in relapses of chemotherapy-sensitive non-Hodgkin's lymphoma. *N Engl J Med* 1995;333:1540-5.

Porter D, Hwang W, Frey N, et al. Chimeric antigen receptor T cells persist and induce sustained remissions in relapsed refractory chronic lymphocytic leukemia. *Science Translational Medicine* 2015 Sept;7(303):1-12.

Prahalad S, Bove K, Dickens D, et al. Etanercept in the treatment of macrophage activation syndrome. *J Rheumatol* 2001;28(9):2120-2124.

Putter H, Fiocco M, Geskus R. Tutorial in biostatistics: Competing risks and multi-state models. Statistics in Medicine 2007;26(11):2389-2430.

Savage K, Al-Rajhi N, Voss N, et al. Favorable outcome of primary mediastinal large B-cell lymphoma in a single institution: the British Columbia experience. *Ann Oncol* 2006;17:123–130.

Sehn L, Antin J, Shulman L, et al. Primary diffuse large B-cell lymphoma of the mediastinum: outcome following high-dose chemotherapy and autologous hematopoietic cell transplantation. *Blood* 1998;91:717–723.

Seshadri T, Kuruvilla J, Crump M, et al. Salvage therapy for relapsed/refractory diffuse large B cell lymphoma. *Biol Blood Marrow Transplant* 2008 Mar;14(3):259-67.

Schuster S, Svoboda J, Nasta S, et al. Phase IIa trial of chimeric antigen receptor modified T cells directed against CD19 (CTL019) in patients with relapsed or refractory CD19+ lymphomas. 2015 ASCO: abstract 8516

Surveillance, Epidemiology, and End Results (SEER) Program Populations (1969-2012) (www.seer.cancer.gov/popdata), National Cancer Institute, DCCPS, Surveillance Research Program, Surveillance Systems Branch, released March 2014.

Song Y, Chi G. A method for testing a pre-specified subgroup in clinical trials. *Statistics in Medicine* 2007;26:3535-3549.

Teachey D, Rheingold S, Maude S, et al. Cytokine release syndrome after blinatumomab treatment related to abnormal macrophage activation and ameliorated with cytokine-directed therapy. *Blood* 2013 June;121(26):5154-5157.

Telio D, Fernandes K, Ma C, et al. Salvage chemotherapy and autologous stem cell transplant in primary refractory diffuse large B-cell lymphoma: outcomes and prognostic factors. *Leukemia & Lymphoma* 2012 May;53(5):836-841.

Turtle

Van Den Neste E, Schmitz N, Nounier N, et al. Outcome of patients with relapsed diffuse large B-cell lymphoma who fail second-line salvage regimens in the international CORAL study. *Bone Marrow Translplant* 2016 Jan; 51(1): 51-7.

Wang S, O'Neill R, Hung H. Approaches to evaluation of treatment effect in randomized clinical trials with genomic subset. *Pharmaceutical Statistics* 2007;6:227-244.

Appendices

Appendix A - Revised IWG Response Criteria for Malignant Lymphoma (Cheson 2007).

Complete Remission (CR): CR requires all of the following:

- Complete disappearance of all detectable clinical evidence of disease and disease-related symptoms if present before therapy.
- Typically FDG-avid lymphoma (large cell, mantle cell and follicular lymphomas are all typically FDG-avid): in subjects with no pretreatment PET scan or when the PET scan was positive before therapy, a post-treatment residual mass of any size is permitted as long as it is PET negative.
- Variably FDG-avid lymphomas/FDG avidity unknown: in subjects without a pretreatment PET scan, or if a pretreatment PET scan was negative, all lymph nodes and nodal masses must have regressed to normal size (≤ 1.5 cm in greatest diameter if > 1.5 cm before therapy). Previously involved nodes that were 1.1 to 1.5 cm in their long axis and more than 1 cm in their short axis before treatment must have decreased to ≤ 1.0 cm in their short axis after treatment.
- The spleen and/or liver, if considered to be enlarged before therapy on basis of physical exam or CT scan, must should be normal size on CT scan and not be palpable on physical examination and nodules thought to represent lymphoma must no longer be present.
- A bone marrow aspirate and biopsy is performed only when the patient had bone marrow involvement with lymphoma prior to therapy or if new abnormalities in the peripheral blood counts or blood smear cause clinical suspicion of bone marrow involvement with lymphoma after treatment. The bone marrow aspirate and biopsy must show no evidence of disease by morphology or if indeterminate by morphology it must be negative by immunohistochemistry. The biopsy core sample must be a minimum of 20 mm in length.

Partial Remission (PR): PR requires all of the following:

- ≥ 50% decrease in sum of the product of the diameters (SPD) of up to 6 of the largest dominant nodes or nodal masses. Dominant nodes or nodal masses should be clearly measurable in at least 2 perpendicular dimensions, should be from different regions of the body if possible and should include mediastinal and retroperitoneal nodes if possible.
- No increase in size of nodes, liver or spleen and no new sites of disease.
- If multiple splenic and hepatic nodules are present, they must regress by ≥ 50% in the SPD. There must be a > 50% decrease in the greatest transverse diameter for single nodules.
- Bone marrow is irrelevant for determination of a PR. If patient has persistent bone marrow involvement and otherwise meets criteria for CR the patient will be considered a PR.
- Typically FDG-avid lymphoma: for subjects with no pretreatment PET scan or if the PET scan was positive before therapy, the post-treatment PET scan should be positive in at least one previously involved site. Note: in subjects with follicular lymphoma or mantle-cell lymphoma, a PET scan is only indicated in subjects with one or at most two residual masses that have regressed by 50% on CT scan.

Stable Disease (SD):

- Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD. PET should be positive in typically FDG-avid lymphomas.

Progressive Disease:

Defined by at least one of the following:

- ≥ 50% increase from nadir in the sum of the products of at least two lymph nodes, or if a single node is involved at least a 50% increase in the product of the diameters of this one node.
- Appearance of a new lesion greater than 1.5 cm in any axis even if other lesions are decreasing in size
- Greater than or equal to a 50% increase in size of splenic or hepatic nodules
- At least a 50% increase in the longest diameter of any single previously identified node more than 1 cm in its short axis.
- Lesions should be PET positive in typically FDG-avid lymphomas unless the lesion is too small to be detected by PET (<1.5 cm in its long axis by CT)

Summary of Changes in KTE-C19-101 (ZUMA-1)

Study Protocol Version 1 (Amendment #5)

The KTE-C19-101 Study Protocol was amended 5 times; amendment 1 was dated 20 Jan 2015; amendment 5 was dated 12 Aug 2016. A summary of major changes implemented with each protocol amendment is provided in the Table below:

Summary of Major Changes Implemented with Each Protocol Amendment

Number and Date	Major Changes
Amendment 1; 20 Jan 2015	Visit windows for screening, leukapheresis, and Month 1 imaging were expanded to provide greater logistical flexibility for the subjects and study sites. Additional toxicity assessments prior to the infusion of axicabtagene ciloleucel were added. Recovery criteria for discharge of subject from hospital after Day 7 were expanded. Grade 3 or higher CRS was designated for expedited safety reporting. Target leukapheresis yield was changed from 2 to10 x 10^9 WBC to 5 to 10 x 10^9 mononuclear cells.
Amendment 2; 27 Feb 2015	Total sample size of the study was increased from approximately 118–124 to 118–136 subjects based upon the contingency for additional cohort assessment in Phase 1. Exclusion criterion was added for subjects with a history of aminoglycoside hypersensitivity. Cyclophosphamide dose for the initial A1 cohort in Phase 1 was increased from 300 to 500 mg/m^2/day. Contingency for an additional cohort (B1) added in the event that a more intensive lymphodepletion therapy is deemed warranted. Subjects would receive 30 mg/kg cyclophosphamide Days –7 and -6 and 25 mg/m^2 fludarabine Days –5 through –1. Objective response rate, the primary endpoint of Phase 2, was specified to be based on investigator assessment; response rate according to the central reviewer was designated as a secondary endpoint.
Amendment 3; 27 Oct 2015	Enrollment was aligned with the day of leukapheresis. Interval between prior therapies and planned day of leukapheresis was reworded.

	Definition of “chemotherapy-refractory disease” criterion was expanded. Changes in toxicity management in response to DLT in Phase 1 (see Section 12.2.3.1). Inclusion criterion for platelet count was changed from 50 to 75 x 10^9/L.ALC min to > 100/μL; replacing serum creatinine with CrCl > 60 mL/min; added no clinical significant pleural effusion. Eligibility criteria governing renal, hepatic, cardiac, pulmonary function were revised (adding oxygen saturation of > 92%, adding cardiac and pleural effusion criteria). Deep vein thrombosis and pulmonary embolism were added as exclusion criteria. Clarified exclusion criteria related to baseline infection (permitted simple urinary tract infections and uncomplicated bacterial pharyngitis if responding to active treatment, excluded uncontrolled or infections requiring intravenous [IV] antimicrobials). Clarification that indwelling line or drain were exclusion criteria but Ommaya reservoir and dedicated central venous access catheters were permitted. Clarifications were made for the concomitant use of corticosteroids and other agents with immunosuppressive potential for the management of CRS and neurologic events. Expanded instructions were given for management of possible hypotension and renal insufficiency arising from CRS; specifically, use of IV saline was detailed. Blood samples were added for measurement of cytokine levels, CRP, and antibodies to axicabtagene ciloleucel or bovine serum albumin. Expanded instructions were given about subject requirements prior to initiating leukapheresis; namely, no significant infection before proceeding with leukapheresis. Clinical safety requirements for subjects to receive conditioning chemotherapy were added. For CRP ≥ 100 mg/dL, the Medical Monitor was to be contacted before proceeding with conditioning chemotherapy. Clinical safety requirements about requirements prior to initiating axicabtagene ciloleucel infusion were added as related to treatment of an active infection Also, for temperature ≥ 38.0 C the Medical Monitor was to be contacted before proceeding with axicabtagene ciloleucel. Instructions were added to educate subjects, families, and caregivers about the development of CRS or neurologic events for after discharge.

	Provisions were added for collecting archived tumor tissue and optional posttreatment fresh tumor tissue. Bone marrow aspirate and biopsy were added to confirm a potential CR to treatment. Optional collection of cerebral spinal fluid by lumbar puncture was added for subjects with new onset ≥ Grade 2 neurologic toxicity to allow further safety assessments. Duration of response to the initial infusion of axicabtagene ciloleucel was added as an additional exploratory endpoint. Instructions were added for subjects eligible to receive a second treatment with axicabtagene ciloleucel.
Amendment 4; 18 Apr 2016	IND and EudraCT numbers added to title page. Several eligibility criteria in Section 5 were clarified as related to prior radiation or systemic therapy, history of hepatitis B or C, history of CNS lymphoma, and history of autoimmune disease. Section 6 was updated with additional toxicity management guidance to include specific treatments for CRS, management of cardiac toxicity, management of neurologic events, deep vein thrombosis prophylaxis. Description of histiocytosis haematophagic/hemophagocytic lymphohistiocytosis (HLH) was added. Lumbar puncture when expect expansion, infiltration of the CAR T cells, and neurologic events were added. Text was added in section 7.11 to include optional paired lumbar punctures for the purpose of collection of cerebral spinal fluid at baseline and after infusion of axicabtagene ciloleucel. Confirmation of eligibility with PET-CT. Recommendation that CRP, ferritin, and LDH (if elevated at baseline) be monitored daily starting at Day 0 through hospitalization. Minor grammatical corrections, protocol inconsistencies and re-ordering of protocol sub-sections were updated to more accurately depict study requirements in a chronological order.
Amendment 5; 12 Aug 2016	Section 3 was updated with addition of Cohort 3. Section 5 was updated with inclusion criteria specific to Cohort 3. Section 6 was updated with rationale and prophylaxis regimen for Cohort 3 as well as updated toxicity management guidance to include monitoring with continuous cardiac telemetry and pulse oximetry and specifying treatment for neurologic events.

	Instructions were added to educate subjects, families, and caregivers about the development of late onset neurologic events after discharge. Section 7 was updated to include pre- and post-dose lumbar punctures as well as EQ-5D questionnaire for subjects assigned to Cohort 3. Retreatment language also clarified. The schedule of assessments was updated to include EQ-5D at screening, Week 4, Month 3, and Month 6, lumbar punctures at baseline, Day 5, and Week 4, tocilizumab at Day 2, and levetiracetam starting at Day 0. Section 10 was updated to include endpoints for Cohort 3 and clarification of the study analyses with regards to Cohort 3. Minor grammatical corrections, protocol inconsistencies, and re-ordering of protocol subsections were updated to more accurately depict study requirements in a chronological order.

Abbreviations: ALC, absolute lymphocyte count; CRS, cytokine release syndrome; CrCl, creatinine clearance; CRP, c-reactive protein; IND, investigational new drug; EQ-5D, European quality of life-5 dimensions; IV, intravenous; LDH, lactate dehydrogenase; WBC, white blood cell.